Express Mail Label No. Date

Docket No.: 03269/100M292-US3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kenneth Newman *et al.*

Confirmation No.: 1944

Application No.: 10/725,246

Art Unit: 1617

Filed: December 1, 2003

Examiner: S. Wang

For: METHOD OF TREATING ACUTE PAIN WITH IBUPROFEN AND OXYCODONE

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. §1.102

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a petition pursuant to 37 C.F.R. §1.102(d) and M.P.E.P. §708.02(VIII) to advance the above-identified patent application out of turn for examination. This petition is accompanied by a Second Preliminary Amendment and a check for $130.00 to cover the fee set forth in 37 C.F.R. §1.17(h).

I. Claims Directed to a Single Invention

It is believed that the claims pending in this application, after entry of the Preliminary Amendment filed November 24, 2004 and the Second Preliminary Amendment filed herewith, are directed to a single invention. The present application includes six independent claims, namely, claims 3, 5, 7, 11, 16, and 19. All of the claims recite an oral dosage form containing oxycodone and ibuprofen. The amount of oxycodone in the claims ranges from about 5 to about 10 mg and the

amount of ibuprofen ranges from about 350 to about 500 mg, with claims 3, 5, 16, and 19 reciting dosage forms containing 5 or 10 mg of oxycodone and 400 mg of ibuprofen.

More specifically, claims 3 and 5 are directed to a method of treating acute pain in a patient in need thereof by orally administering an effective amount of oxycodone and ibuprofen in one oral dosage form at least once a day to provide partial or complete pain relief within 30 minutes. The dosage form comprises about 5 mg (claim 3) or about 10 mg (claim 5) of oxycodone or a pharmaceutically acceptable salt thereof and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof (based on the weights of molar equivalents of oxycodone hydrochloride and ibuprofen, respectively).

Claim 7 is also directed to a method of treating acute pain in a patient in need thereof by orally administering an oral dosage form of oxycodone and ibuprofen. Claim 7 specifies that the dosage form comprises from about 5 to about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof and from about 350 to about 500 mg of ibuprofen or a pharmaceutically acceptable salt thereof.

Claim 11 is directed to a method for accelerating onset of pain relief in acute postoperative pain experienced by a patient post-anesthesia by administering to the patient an oral dosage form comprising from about 5 to about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof and from about 350 to about 500 mg of ibuprofen or a pharmaceutically acceptable salt thereof.

Claim 16 and 19 are directed to oral unitary dosage forms comprising about 5 or 10 mg of oxycodone or a pharmaceutically acceptable salt thereof and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof.

If the Examiner determines that all pending claims are not directed to a single invention, applicants will make an election without traverse as a prerequisite to the grant of special status.

II. Pre-Examination Search

A pre-examination search was made in U.S. Classes 514/282 and 514/570 by the U.S. Patent and Trademark Office, as the International Searching Authority for the International counterpart (PCT Application No. PCT/US03/38088) to this application. The International Searching Authority conducted a search of original claims 1-14 in the International counterpart to the present application (International Publication No. WO 2004/050025, Exhibit 1). Original claims 2-11 of the International application are identical to pending claims 2-11 (except pending claims 3 and 5 are in independent form, pending claims 2, 9, and 10 depend from claims 3 and 7, and pending claim 11 specifies that the oral dosage form comprises from about 350 to about 500 mg of ibuprofen, rather than a weight ratio of ibuprofen to oxycodone of 20:1 to 100:1).

The International Search Report and the three documents cited therein are attached as Exhibits 2-5, respectively.

A search was also performed on the MicroPatent PatSearch database, which includes U.S., European, Japanese, German, UK, and French patents and published applications as well as International patent publications for the terms "oxycodone" and "ibuprofen" in the claims, title and abstract. The references uncovered by these searches were submitted with the July 15, 2004 and January 7, 2005 Information Disclosure Statements.

Below is a discussion of the references cited in the search report as well as two articles submitted with the July 15, 2004 Information Disclosure Statement, demonstrating how the claimed invention is patentable over each of them. The remaining prior art references are believed to be cumulative of these references.

III. Discussion of References

A. U.S. Patent No. 4,569,937 ("the '937 Patent", Exhibit 3)

The '937 Patent discloses a pharmaceutical composition containing a synergistic effective analgesic amount of oxycodone and ibuprofen.

The '937 Patent does not disclose or suggest treating *acute* pain (claims 3, 5, and 7) or accelerating onset of pain relief in acute postoperative pain experienced by a patient post-anesthesia (claim 11) by orally administering an oral dosage form containing from about 5 to about 10 mg of oxycodone and from about 350 to about 500 mg of ibuprofen.

According to the book *Basics of Anesthesia*, 4th Ed., R. K. Stoelting and R. D. Miller (2000), p. 428 (Exhibit 8), oral analgesics are not typically administered for moderate and severe acute pain when fast pain relief is a primary goal:

> "Oral administration of analgesics is not considered optimal for management of moderate to severe acute postoperative pain, principally because of the lack of titratability and prolonged time to peak effect. Traditionally, postoperative patients are switched [from parenteral analgesics] to oral analgesics (aspirin, acetaminophen, NSAIDs) when pain has diminished to the extent that the need for rapid adjustments in the level of analgesia is unlikely. ... [T]here is a growing need for oral analgesics that are efficacious in the treatment of moderate to severe acute postoperative pain."

Applicants unexpectedly discovered that administration of an oral dosage form containing about 5 to about 10 mg of oxycodone and from about 350 to about 500 mg of ibuprofen provides earlier onset of pain relief than administration of each active ingredient alone, thus rendering the dosage form particularly suitable for the treatment of acute pain. *See*, for example, Figure 4 and Example 8 of the instant application wherein the maximum ibuprofen plasma concentration with the unitary dosage form is achieved earlier as compared to concurrent administration of separate dosage forms of oxycodone and ibuprofen; and Figures 12 and 13 and Example 10 which show that a unitary dosage form containing both oxycodone and ibuprofen have a faster oxycodone dissolution rate and result in more rapid absorption of oxycodone.

The '937 Patent does not disclose or suggest that such an oral dosage form could provide an earlier onset of pain relief. In fact, no *in vivo* studies involving an oral dosage form containing both ibuprofen and oxycodone are described in the '937 Patent. Rather, the '937 Patent only reports the results of a study in which mice were *sequentially* administered oral solutions of oxycodone and ibuprofen. *See* col. 8, lines 50-61, of the '937 Patent.

Furthermore, the '937 Patent does not disclose an oral dosage form containing about 5 or 10 mg of oxycodone or a pharmaceutically acceptable salt thereof and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof.

Therefore, the '937 Patent does not disclose or suggest the methods of treating acute pain recited in claims 2-10 and 22, the method for accelerating onset of pain relief in acute postoperative pain experienced by a patient post-anesthesia recited in claims 11 and 23, or the oral unitary dosage

forms recited in claims 16-21. Accordingly, claims 2-11 and 16-23 are patentable over the '937 Patent.

B. U.S. Patent No. 4,464,376 ("the '376 Patent", Exhibit 4)

The '376 Patent discloses a composition comprising caffeine together with a selected non-narcotic analgesic/non-steroidal anti-inflammatory drug or a selected narcotic analgesic, or both. *See* abstract. The caffeine is said to enhance the analgesic or anti-inflammatory response of the non-narcotic analgesic/non-steroidal anti-inflammatory drug or the narcotic analgesic, and to hasten its onset. *Id.* The '376 Patent does not disclose or suggest an oral dosage form containing from about 5 to about 10 mg of oxycodone and from about 350 to about 500 mg of ibuprofen. The patent also does not disclose or suggest that this combination of ibuprofen and oxycodone in a single dosage form will hasten the onset of pain relief compared to administration of either active ingredient alone or concurrent administration of both active ingredients in separate dosage forms.

Claims 2-11 and 16-23 are therefore patentable over the '376 Patent.

C. European Patent Publication No. 68838 ("EP '838") (Exhibit 5)

EP '838 discloses a process for the management of pain by administering a narcotic analgesic and ibuprofen or flurbiprofen, or a salt or ester thereof. *See* abstract. EP '838 does not disclose or suggest an oral dosage form containing from about 5 to about 10 mg of oxycodone and from about 350 to about 500 mg of ibuprofen. EP '838 also does not disclose or suggest that this combination of ibuprofen and oxycodone in a single dosage form will hasten the onset of pain relief compared to

administration of either active ingredient alone or concurrent administration of both active ingredients in separate dosage forms.

Claims 2-11 and 16-23 are therefore patentable over EP '838.

D. Cooper et al., Clinical Pharmacology & Therapeutics (1993) ("Cooper") (Exhibit 6)

Cooper reports the results of a clinical study where (1) 2 x 200 mg ibuprofen capsules with a 5 mg oxycodone capsule, (2) 2 x 200 mg ibuprofen capsules and a placebo capsule, or (3) 3 placebo capsules were administered to patients having pain due to surgical removal of impacted teeth.

Cooper does not disclose or suggest administration of oxycodone and ibuprofen in a single dosage form, nor its use to treat acute pain. Furthermore, as discussed above, applicants unexpectedly discovered that administration of an oral dosage form containing about 5 to about 10 mg of oxycodone and from about 350 to about 500 mg of ibuprofen provides an earlier onset of pain relief than concurrent administration of separate dosage forms of oxycodone and ibuprofen. *See*, for example, Figure 4 and Example 8 of the instant application wherein the maximum ibuprofen plasma concentration with the unitary dosage form is achieved earlier as compared to concurrent administration of separate dosage forms of oxycodone and ibuprofen; and Figures 12 and 13 and Example 10 which show that a unitary dosage form containing both oxycodone and ibuprofen have a faster oxycodone dissolution rate and result in more rapid absorption of oxycodone.

Claims 2-11 and 16-23 are therefore patentable over Cooper.

E. **Dionne, *J. Oral Maxillofac Surg.*, 57:673-678 (1999) ("Dionne") (Exhibit 7)**

Dionne discloses the results of a study in which patients were administered 400 mg of ibuprofen alone or in conjunction with a second dosage form containing 2.5, 5, or 10 mg of oxycodone after surgical removal of two to four impacted third molars.

Dionne does not disclose or suggest administration of oxycodone and ibuprofen in a single dosage form, nor its use to treat acute pain. Furthermore, as discussed above, applicants unexpectedly discovered that administration of an oral dosage form containing about 5 to about 10 mg of oxycodone and from about 350 to about 500 mg of ibuprofen provides an earlier onset of pain relief than concurrent administration of separate dosage forms of oxycodone and ibuprofen. *See*, for example, Figure 4 and Example 8 of the instant application wherein the maximum ibuprofen plasma concentration with the unitary dosage form is achieved earlier as compared to concurrent administration of separate dosage forms of oxycodone and ibuprofen; and Figures 12 and 13 and Example 10 which show that a unitary dosage form containing both oxycodone and ibuprofen have a faster oxycodone dissolution rate and result in more rapid absorption of oxycodone.

Claims 2-11 and 16-23 are therefore patentable over Dionne.

III. Conclusion

In view of the foregoing, the PTO is requested to make this application special and to accelerate examination pursuant to 37 C.F.R. § 1.102(d) and M.P.E.P. §708.02(VIII).

Favorable action is earnestly solicited.

Dated: May 25, 2005

Respectfully submitted,

By _____
Jay P. Lessler
Registration No.: 41,151
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Applicant

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050025 A3

(51) International Patent Classification[7]: A61K 31/44, 31/19

(21) International Application Number:
PCT/US2003/038088

(22) International Filing Date:
26 November 2003 (26.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/429,944	29 November 2002 (29.11.2002)	US
60/453,044	7 March 2003 (07.03.2003)	US
60/506,632	26 September 2003 (26.09.2003)	US

(71) Applicant *(for all designated States except US)*: **FOREST LABORATORIES, INC.** [US/US]; 909 Third Avenue, New York, NY 10022-4371 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NEWMAN, Kenneth** [US/US]; 20 Sunderland Lane, Katonah, NY 10536 (US). **ABRAMOTWITZ, Wattanaporn** [US/US]; 4 Abbington Lane, West Windsor, NJ 08550 (US). **DAVILA-ZAVALA, Pablo** [US/US]; 130 Woods Road, East Windsor, NJ 08520 (US). **GRILL, Andreas** [US/US]; 5 June Street, Hauppauge, NJ 11788 (US). **TANG, Fuxing** [US/US]; 142 Claremont Street, Deer Park, NY 11729 (US).

(74) Agent: **LESSLER, Jay. P.**; Darby & Darby P.C., P.O. Box 5257, New York, NY 10150-5257 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
9 December 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATION OF IBUPROFEN AND OXYCODONE FOR ACUTE PAIN RELIEF

(57) Abstract: The present invention is a method of achieving fast onset of pain relief for acute pain in a patient in need thereof comprising orally administering a unitary formulation (or oral dosage form) containing an effective analgesic amount of (a) oxycodone or a pharmaceutically acceptable salt thereof and (b) ibuprofen or pharmaceutically acceptable salt thereof. Preferably, the unitary formulation contains (a) oxycodone or a pharmaceutically acceptable salt thereof and (b) ibuprofen or a pharmaceutically acceptable salt thereof at a weight ratio of from about 1:20 to about 1:100 and more preferably about 1:40 to about 1:80, based on the weights of molar equivalents of oxycodone hydrochloride and ibuprofen, respectively. Preferably, an amount of oxycodone and ibuprofen effective to provide partial or complete pain relief within 30 minutes is administered. More preferably, the amount is sufficient to provide partial or complete pain relief within 25 minutes. It has been discovered that administration of an oral dosage form containing both oxycodone and ibuprofen provides earlier onset of pain relief than administration of either active ingredient alone. Moreover, the earlier onset of pain relief may be attributable at least in part to administration of a single dosage form containing both active ingredients as opposed to administering oxycodone and ibuprofen in separate oral dosage forms (i.e., administration of a first dosage form containing oxycodone and a second dosage form containing ibuprofen). The method of the present invention is particularly useful for treating acute postoperative pain, including, but not limited to, moderate and/or severe acute postoperative pain (such as that resulting from dental surgery).

WO 2004/050025 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/38088

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/44, 31/19
US CL : 514/282, 570
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/282, 570

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,569,937 A (BAKER et al.) 11 February 1986 (11.02.1986) the entire documents, particularly, example 1-6, table 1 and the claims.	1, 11, --- 2-10, 12-14
Y	US 4,464,376 A (SUNSHINE et al) 07 August 1984 (07.08.1984), the entire documents, particularly, claims 18-25.	1-14
Y	EP 0 068 838 A1 (THE UPJOHN COMPANY) 05 January 1983 (05.01.1983), see the entire document	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
30 September 2004 (30.09.2004)

Date of mailing of the international search report
21 OCT 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Shengjun Wang

Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US03/38088

Continuation of Item 4 of the first sheet:
The title is too long, PCT Rule 4.3. New Title:

"Combination of Ibuprofen and Oxycodone for Acute pain Relief "

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE MEDLINE BIOSIS, search terms: oxycodone, ibuprofen, combination, synergistic, analgesic, pain, acute pain

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050025 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2003/038088

(22) International Filing Date:
26 November 2003 (26.11.2003)

(25) Filing Language: English

(26) Publication Language: English

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(71) Applicant *(for all designated States except US)*: **FOREST LABORATORIES, INC.** [US/US]; 909 Third Avenue, New York, NY 10022-4371 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **NEWMAN, Kenneth** [US/US]; Katonah, New York (US).

(74) Agent: **LESSLER, Jay. P.**; Darby & Darby P.C., P.O. Box 5257, New York, NY 10150-5257 (US).

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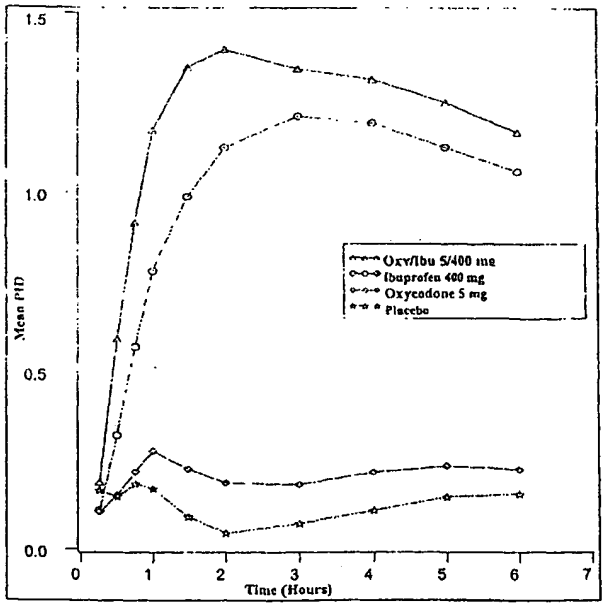
(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,

[Continued on next page]

(54) Title: METHOD OF TREATING ACUTE PAIN WITH A UNITARY DOSAGE FORM COMPRISING IBUPROFEN AND OXYCODONE

Figure 1. Analysis of Pain Intensity Difference (PID) Scores Over Time



(57) Abstract: The present invention is a method of achieving fast onset of pain relief for acute pain in a patient in need thereof comprising orally administering a unitary formulation (or oral dosage form) containing an effective analgesic amount of (a) oxycodone or a pharmaceutically acceptable salt thereof and (b) ibuprofen or pharmaceutically acceptable salt thereof. Preferably, the unitary formulation contains (a) oxycodone or a pharmaceutically acceptable salt thereof and (b) ibuprofen or a pharmaceutically acceptable salt thereof at a weight ratio of from about 1:20 to about 1:100 and more preferably about 1:40 to about 1:80, based on the weights of molar equivalents of oxycodone hydrochloride and ibuprofen, respectively. Preferably, an amount of oxycodone and ibuprofen effective to provide partial or complete pain relief within 30 minutes is administered. More preferably, the amount is sufficient to provide partial or complete pain relief within 25 minutes. It has been discovered that administration of an oral dosage form containing both oxycodone and ibuprofen provides earlier onset of pain relief than administration of either active ingredient alone. Moreover, the earlier onset of pain relief may be attributable at least in part to administration of a single dosage form containing both active ingredients as opposed to administering oxycodone and ibuprofen in separate oral dosage forms (i.e., administration of a first dosage form containing oxycodone and a second dosage form containing ibuprofen). The method of the present invention is particularly useful for treating acute postoperative pain, including, but not limited to, moderate and/or severe acute postoperative pain (such as that resulting from dental surgery).

WO 2004/050025 A2

SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHOD OF TREATING ACUTE PAIN WITH A UNITARY DOSAGE FORM COMPRISING IBUPROFEN AND OXYCODONE

[01] This application claims the benefit of U.S. Provisional Patent Application No. 60,429,944, filed November 29, 2002, U.S. Provisional Patent Application No. 60/453,044, filed March 7, 2003, and U.S. Provisional Patent Application No. 60/506,632, filed September 26, 2003, all of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[02] The present invention relates to a method of treating acute pain (e.g., acute postoperative pain) by administering a composition comprising ibuprofen and oxycodone, whereby a faster onset of pain relief is achieved.

BACKGROUND OF THE INVENTION

[03] Oral analgesics, such as ibuprofen (U.S. Patent Nos. 3,228,831 and 3,385,886), and narcotic analgesics (e.g., oxycodone), have been known for decades. Narcotic analgesics, however, can be addictive and subjected to abuse by parenteral administration. As a result, there has been research in reducing the dosage of narcotic analgesics necessary to obtain pain relief. For example, U.S. Patent No. 4,569,937 discloses

an analgesic pharmaceutical composition containing a synergistic effective amount of oxycodone and ibuprofen.

[04] Oral analgesics are not typically administered for moderate and severe acute pain when fast pain relief is a primary goal. As noted in *Basics of Anesthesia*, 4th Ed., R. K. Stoelting and R. D. Miller (2000), p. 428:

> "Oral administration of analgesics is not considered optimal for management of moderate to severe acute postoperative pain, principally because of the lack of titratability and prolonged time to peak effect. Traditionally, postoperative patients are switched [from parenteral analgesics] to oral analgesics (aspirin, acetaminophen, NSAIDs) when pain has diminished to the extent that the need for rapid adjustments in the level of analgesia is unlikely. ... [T]here is a growing need for oral analgesics that are efficacious in the treatment of moderate to severe acute postoperative pain."

[05] Cooper et al., *Clinical Pharmacology & Therapeutics*, PII-9 (February 1993), report the results of a clinical study where (1) 2 x 200 mg ibuprofen capsules with a 5 mg oxycodone capsule, (2) 2 x 200 mg ibuprofen capsules and a placebo capsule, or (3) 3 placebo capsules were administered to patients having pain due to surgical removal of impacted teeth. See also Dionne, *J. Oral Maxillofac Surg.*, 57:673-678 (1999).

[06] There is a need for an oral analgesic which provides fast pain relief.

SUMMARY OF THE INVENTION

[07] The present invention is a method of achieving fast onset of pain relief for acute pain in a patient in need thereof comprising orally administering a unitary formulation (or oral dosage form) containing an effective analgesic amount of (a) oxycodone or a pharmaceutically acceptable salt thereof and (b) ibuprofen or a pharmaceutically acceptable salt thereof. Preferably, the unitary formulation contains (a) oxycodone or a pharmaceutically acceptable salt thereof and (b) ibuprofen or a pharmaceutically acceptable salt thereof at a weight ratio of from about 1:20 (based on the weight of a molar equivalent of oxycodone hydrochloride and the free acid of ibuprofen, respectively) to about 1:100 and more preferably about 1:40 to about 1:80. Preferably, an amount of oxycodone and ibuprofen effective to provide partial or complete pain relief within 30 minutes is administered. More preferably, the amount is sufficient to provide partial or complete pain relief within 25 minutes. It has been discovered that administration of an oral dosage form containing both oxycodone and ibuprofen provides earlier onset of pain relief than administration of either active ingredient alone. Moreover, the earlier onset of pain relief may be attributable at least in part to administration of a single dosage form containing both active ingredients as opposed to administering oxycodone and ibuprofen in separate oral dosage forms (i.e., administration of a first dosage form containing oxycodone and a second dosage form containing ibuprofen). The method of the present invention is particularly useful for treating acute postoperative pain, including, but not limited to, moderate and/or severe acute postoperative pain (such as that resulting from dental surgery).

[08] According to one preferred embodiment, the oral dosage form comprises from about 5 to about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof (based on the weight of a molar equivalent of oxycodone hydrochloride and the free

acid of ibuprofen, respectively) and from about 350 to about 500 mg of ibuprofen or a pharmaceutically acceptable salt thereof. For example, the oral dosage form may comprise about 5 mg of oxycodone or a pharmaceutically acceptable salt thereof (such as oxycodone HCl) and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof. Another example is an oral dosage form which comprises about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof (such as oxycodone HCl) and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof.

[09] The present invention also provides a method of treating acute pain in a patient in need thereof by orally administering an oral dosage form comprising from about 5 to about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof and from about 350 to about 500 mg of ibuprofen or a pharmaceutically acceptable salt thereof. According to a preferred embodiment, the oral dosage form comprises about 5 or about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof (such as oxycodone HCl) and about 400 mg of ibuprofen.

[10] Yet another embodiment is a method for accelerating onset of pain relief in acute postoperative pain experienced by a patient post-anesthesia by administering to the patient an oral dosage form comprising (a) ibuprofen or a pharmaceutically acceptable salt thereof and (b) oxycodone or a pharmaceutically acceptable salt thereof (such as oxycodone HCl), at a weight ratio within the range of 20:1 to 100:1. Preferably, the weight ratio ranges from about 40:1 to about 80:1. The oral dosage form contains from about 5 to about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof. The term "post-anesthesia" refers to a patient previously anaesthetized who is suffering from pain after the anesthesia partially or completely fades or wears off.

[11] Unexpectedly, treatment of acute pain according to the present invention, i.e., administering to a subject experiencing such pain a unitary dosage form containing oxycodone and ibuprofen, results in a statistically significant earlier onset of pain relief than administration of either ingredient alone. A single dosage form has been shown to have a different (faster) ibuprofen pharmacokinetic profile, which is consistent with a significantly earlier onset of pain relief. See Figure 4 and Example 8 wherein the maximum ibuprofen plasma concentration with the unitary dosage form is achieved earlier as compared to the two dosage form combination. Furthermore, a single dosage form has been shown to have a faster oxycodone dissolution rate and result in more rapid absorption of oxycodone. See Figures 12 and 13 (30-60 minutes) and Example 10.

[12] The unitary dosage form of the present invention also permits the use of higher amounts of ibuprofen in the dosage form without a deterrent increase of the side-effects attendant to administration of this analgesic.

[13] Yet another embodiment is a unitary dosage form comprising (a) oxycodone or a pharmaceutically acceptable salt thereof, (b) ibuprofen or a pharmaceutically acceptable salt thereof, and (c) an anti-picking effective amount of silicified microcrystalline cellulose. The unitary dosage form may be prepared by direct compression or wet granulation. The tablet preferably has a hardness of from about 12 to about 18 kp.

[14] A preferred directly compressed unitary dosage form of the present invention comprises (a) from about 0.7 to about 1.7% by weight of oxycodone or a pharmaceutically acceptable salt thereof (based on the weight of a molar equivalent of oxycodone hydrochloride), (b) from about 64 to about 77% by weight of ibuprofen or a pharmaceutically acceptable salt thereof (based on the weight of a molar equivalent of the free acid of ibuprofen), and (c) from about 15 to about 22% by weight of silicified

microcrystalline cellulose, based upon 100% total weight of the directly compressed unitary dosage form.

BRIEF DESCRIPTION OF THE DRAWINGS

[15] Figures 1-3 show the pain intensity difference (PID), pain relief (PR) scores, and combined pain relief and pain intensity difference (PRID), respectively, over 6 hours for the pooled data from the two clinical studies described in Example 7 for 5 mg oxycodone HCl/400 mg ibuprofen, 400 mg ibuprofen, 5 mg oxycodone HCl, and placebo.

[16] Figure 4 shows a graph of the ibuprofen plasma concentration (μg/mL) versus time (hours) after administration of (1) a 5 mg oxycodone HCl / 400 mg ibuprofen tablet and (2) a 5 mg oxycodone HCl tablet with 2 x 200 mg ibuprofen tablets in Example 8.

[17] Figure 5 shows a graph of the oxycodone plasma concentration (μg/mL) versus time (hours) after administration of (1) a 5 mg oxycodone HCl / 400 mg ibuprofen tablet and (2) a 5 mg oxycodone HCl tablet with 2 x 200 mg ibuprofen tablets in Example 8.

[18] Figure 6 is a bar graph showing the effects of increasing concentrations of ibuprofen on the permeability (Papp) of oxycodone across Caco-2 cell monolayers. The asterisks (*) indicates a significance level of $p < 0.05$, when compared with the permeability value in the absence of ibuprofen.

[19] Figure 7 is a bar graph showing the effects of increasing concentrations of ibuprofen on the amount of oxycodone transported across Caco-2 cell monolayers after the initial 20 minute-transport period. The asterisks (*) indicates a significance level of $p < 0.05$, when compared with the permeability value in the absence of ibuprofen.

[20] Figure 8 is a bar graph showing the effects of increasing concentrations of oxycodone on the permeability (Papp) of ibuprofen across Caco-2 cell monolayers.

[21] Figure 9 is a schematic of the continuous dissolution/Caco-2 system described in Example 10.

[22] Figure 10 is a graph of the percentage by weight of ibuprofen dissolved (mean ± standard deviation, n=3) over 60 minutes from a 400 mg ibuprofen/5 mg oxycodone hydrochloride tablet (♦), 2 Nuprin® tablets (200 mg ibuprofen per tablet) (■), and the combination of 2 Nuprin® tablets (200 mg ibuprofen per tablet) and 1 Roxicodone™ tablet (5 mg oxycodone hydrochloride) (▲) in fasted state simulated intestinal fluid (FaSSIF) buffer as determined by the dissolution procedure described in Example 10.

[23] Figure 11 is a graph of the percentage by weight of ibuprofen absorbed (mean ± standard deviation, n=3) over 60 minutes from a 400 mg ibuprofen/5 mg oxycodone tablet (♦), 2 Nuprin® tablets (200 mg ibuprofen per tablet) (■), and the combination of 2 Nuprin® tablets (200 mg ibuprofen per tablet) and 1 Roxicodone™ tablet (5 mg oxycodone hydrochloride) (▲) in FaSSIF buffer as determined by the dissolution procedure described in Example 10.

[24] Figure 12 is a graph of the percentage by weight of oxycodone dissolved (mean ± standard deviation, n=3) over 60 minutes from 1 tablet of 400 mg ibuprofen/5 mg oxycodone hydrochloride (♦), 1 Roxicodone™ tablet (5 mg oxycodone hydrochloride) (■), and the combination of 2 Nuprin® tablets (200 mg ibuprofen per tablet) and 1 Roxicodone™ tablet (5 mg oxycodone hydrochloride) (▲) in FaSSIF buffer as determined by the dissolution procedure described in Example 10.

[25] Figure 13 is a graph of the percentage by weight of oxycodone absorbed (mean ± standard deviation, n=3) over 60 minutes from 1 tablet of 400 mg ibuprofen/5 mg oxycodone hydrochloride (♦), 1 Roxicodone™ tablet (5 mg oxycodone hydrochloride) (■), and the combination of 2 Nuprin® tablets (200 mg ibuprofen per tablet) and 1 Roxicodone™ tablet (5 mg oxycodone hydrochloride) (▲) in FaSSIF buffer as determined by the dissolution procedure described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

[26] As used herein, the term "about" means within 10% of a given value, preferably within 5%, and more preferably within 1% of a given value. Alternatively, the term "about" means that a value can fall within a scientifically acceptable error range for that type of value, which will depend on how qualitative a measurement can be given the available tools.

[27] All weights and weight ratios specified for oxycodone and pharmaceutically acceptable salts there of are based on the weight of a molar equivalent of oxycodone hydrochloride.

[28] All weights and weight ratios specified for ibuprofen and pharmaceutically acceptable salts thereof are based on the weight of a molar equivalent of the free acid of ibuprofen.

[29] The term "acute pain" refers to pain that lasts or is anticipated to last a short time, typically less than a month. The term "acute pain" includes, but is not limited to, moderate, severe, and moderate to severe acute pain.

[30] The term "acute postoperative pain" refers to acute pain resulting from surgery (such as dental surgery (e.g., molar extraction and in particular third molar extraction)). Acute postoperative pain is a physiologic reaction to tissue injury, visceral distension, or disease.

[31] The term "patient" as used herein refers to a mammal and preferably a human.

[32] The phrase "pharmaceutically acceptable" refers to additives or compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a mammal.

[33] The terms "treat" and "treating" refer to reducing or relieving pain.

[34] As used herein, the terms "effective analgesic amount" and "effective amount" refer to an amount of oxycodone or a pharmaceutically acceptable salt thereof and ibuprofen or a pharmaceutically acceptable salt thereof that, when administered to a mammal for treating pain, is sufficient to treat the pain. The "effective analgesic amount" may vary depending on the severity of pain and the mammal to be treated. Preferably, the amount of oxycodone and ibuprofen administered is effective to provide partial or complete pain relief within 30 minutes of administration. More preferably, the amount is sufficient to provide partial or complete pain relief within 22, 23, 24, 25, 26, 27, 28, or 29 minutes of administration.

[35] Pharmaceutically acceptable salts of oxycodone include, but are not limited to, hydrochlorides, hydrobromides, hydroiodides, sulfates, bisulfates, nitrates, citrates, tartrates, bitartrates, phosphates, malates, maleates, fumarates, succinates, acetates,

terephthalates, and pamoates. A preferred pharmaceutically acceptable salt of oxycodone is oxycodone hydrochloride.

[36] The ibuprofen may be in any form, including ibuprofen USP 90% (DCI-90). Pharmaceutically acceptable salts of ibuprofen include, but are not limited to, ibuprofen salts of aluminum, calcium, potassium, and sodium.

[37] The amount of oxycodone in the dosage forms of the present invention to be administered daily preferably ranges from about 0.025 or 0.05 to about 7.50 milligrams per kilogram of body weight (mg/kg). The amount of ibuprofen in the compositions to be administered daily preferably ranges from about 5 to about 120 milligrams per kilogram of body weight (mg/kg).

[38] Preferably, at least 95% by weight of the oxycodone and pharmaceutically acceptable salts thereof is released from the oral dosage form after 15 minutes in FaSSIF. The maximum plasma concentration of ibuprofen is preferably reached within 1.5 hours after administration of the oral dosage form.

[39] In a preferred embodiment, the oral dosage form contains from about 5 to about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof. For example, the oral dosage form may contain about 5 or about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof (e.g., oxycodone HCl) and 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof. Such an oral dosage form is preferably administered to a patient 1 to 5 times daily and more preferably 1 to 4 times daily. According to one embodiment, such an oral dosage form is administered to a patient for up to 1 week.

[40] The oral dosage forms may be tablets, pills, capsules, caplets, boluses, powders, granules, elixirs, syrups, or suspensions. The oral dosage form is preferably a solid,

such as a tablet, pill, caplet, or capsule. The solid dosage forms may include pharmaceutically acceptable additives, such as excipients, carriers, diluents, stabilizers, plasticizers, binders, glidants, disintegrants, bulking agents, lubricants, plasticizers, colorants, film formers (e.g., Opadry White and Opadry II White), flavouring agents, preservatives, dosing vehicles, and any combination of any of the foregoing. Preferably, these additives are pharmaceutically acceptable additives, such as those described in *Remington's, The Science and Practice of Pharmacy*, (Gennaro, A.R., ed., 19th edition, 1995, Mack Pub. Co.) which is herein incorporated by reference.

[41] When tablets containing ibuprofen and oxycodone hydrochloride were prepared, they exhibited picking defects. See, for example, Example 2A below. In particular, the logo and product identification de-bossing was picked making it difficult to read and less aesthetically pleasing. The term "picking" refers to the removal of material (such as a film fragment) from the surface of a tablet and its adherence to the surface of another object (such as another tablet or a punching machine). See pages 101 and 272 of Pharmaceutical Dosage Forms: Tablets Volume 3, edited by H. A. Lieberman and L. Lachman, Marcel Dekker, Inc. (1982). Picking may occur, for example, when tablets are compressed or tumbled. The material removed may include logos, monograms, lettering, and numbering which were intended to appear on the surface of the tablet.

[42] It was surprisingly found that the inclusion of silicified microcrystalline cellulose in the tablet eliminated picking defects, irrespective of whether the tablets were prepared by direct compression or wet granulation methods. As a result, more expensive printing techniques are not required to prevent the picking defects. The inclusion of a mixture of microcrystalline cellulose and colloidal silicon dioxide rather than silicified microcrystalline cellulose did not, however, eliminate picking defects. It was also found that

the silicified microcrystalline cellulose did not result in any loss of the direct compressibility of the formulation or slow the release of the ibuprofen or oxycodone hydrochloride upon administration.

[43] The term "an anti-picking effective amount" refers to an amount which is sufficient to substantially eliminate picking defects. Preferably, the tablets contain an amount sufficient for them (1) to meet Acceptable Quality Limits (AQL) in accordance with ANSI/ASQC standards and/or (2) to exhibit no significant debassing or logo defects. Preferably, the number of tablets which do not meet AQL in accordance with ANSI/ASQC standards is less than 1% or 0.1% of the tablets produced.

[44] Silicified microcrystalline cellulose acts as a filler and glidant. The term "silicified microcrystalline cellulose" refers to a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1 to about 20% by weight of silicon dioxide, by weight of the microcrystalline cellulose. The microcrystalline cellulose and silicon dioxide in the particulate agglomerate are in intimate association with each other. The silicon dioxide portion of the silicified microcrystalline cellulose is preferably derived from silicon dioxide having an average primary particle size of from about 1 nm to about 100 μm. According to one embodiment, the average primary particle size of the silicon dioxide ranges from about 5 nm to about 40 or 50 μm. "Primary particle size" refers to the size of the particles when not agglomerated.

[45] The silicon dioxide may have a surface area of from about 10 m^2/g to about 500 m^2/g, from about 50 m^2/g to about 500 m^2/g, or from about 175 m^2/g to about 350 m^2/g.

[46] In one embodiment, the silicified microcrystalline cellulose comprises from about 0.5% to about 10% by weight of silicon dioxide, based on 100% total weight of

the microcrystalline cellulose. According to another embodiment, the silicified microcrystalline cellulose comprises from about 1.25% to about 5% by weight of silicon dioxide, based on 100% total weight of the microcrystalline cellulose.

[47] According to one embodiment, the moisture content of the silicified microcrystalline cellulose ranges from about 0.5 to about 2.5 LOD (loss on drying), from about 0.5 to about 1.8 LOD, from about 0.5 to about 1.5% LOD, or from about 0.8 to about 1.2% LOD.

[48] Preferred silicified microcrystalline celluloses include, but are not limited to, those described in U.S. Patent Nos. 5,725,884, 6,103,219, and 6,471,994, all of which are hereby incorporated by reference, and Prosolv SMCC 90 (which is a mixture of colloidal silicon dioxide NF and microcrystalline cellulose NF available from Penwest Pharmaceuticals Co. of Patterson, NJ).

[49] Suitable binders include, but are not limited to, starch, gelatin, sugars (such as sucrose, molasses and lactose), natural and synthetic gums (such as acacia, sodium alginate, carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidone, polyethylene glycol, ethylcellulose, and waxes).

[50] Suitable glidants include, but are not limited to, talc and silicon dioxide (e.g, colloidal silicon dioxide).

[51] Suitable disintegrants include, but are not limited to, starches, sodium starch glycolate, croscarmellose sodium, crospovidone, clays, celluloses (such as purified cellullose, methylcellulose, sodium carboxymethyl cellulose), alginates, pregelatinized corn starches, and gums (such as agar, guar, locust bean, karaya, pectin and tragacanth gums). A preferred disintegrant is sodium starch glycolate.

[52] Suitable bulking agents include, but are not limited to, starches (such as corn starch), microcrystalline cellulose, lactose (e.g., lactose monohydrate), sucrose, dextrose, mannitol, calcium phosphate, and dicalcium phosphate.

[53] Suitable lubricants include, but are not limited to, stearic acid, stearates (such as calcium stearate and magnesium stearate), talc, sodium fumarate, polyethylene glycol, hydrogenated cottonseed, and castor oils.

[54] Preferred tablet formulations include those shown in the table below.

Ingredient	Concentration (percent by weight)	
	Preferred	More Preferred
Ibuprofen	from about 64 to about 77%	from about 70 to about 75%
Oxycodone Hydrochloride	from about 0.7 to about 1.7%	from about 0.7 to about 1.7%
Silicified Microcrystalline Cellulose	from about 15 to about 22%	from about 15 to about 17%
Sodium Starch Glycolate	from about 2.5 to about 4.5%	from about 3.5 to about 4%
Stearic Acid	from about 1.5 to about 3%	from about 2 to about 2.5%
Calcium Stearate	from about 0.5 to about 1.5%	from about 0.6 to about 1%
Coating (e.g. Opadry™)	from about 2 to about 5%	from about 2.5 to about 3.5%

[55] Solid dosage forms may be prepared by mixing the ibuprofen and oxycodone with a pharmaceutically acceptable carrier and any other desired additives, such as by wet or dry granulation. The mixture is typically mixed until a homogeneous mixture of the oxycodone, ibuprofen, carrier, and any other desired additives is formed, i.e., until the active agents are dispersed evenly throughout the mixture. The mixture may be formed into tablets by any method known in the art (e.g., direct compression and wet granulation), including those described in *Pharmaceutical Dosage Forms: Tablets*, H. Liebermand and L. Lachman, 1982, which is hereby incorporated by reference.

[56] The oral dosage forms are preferably formulated as "immediate release" dosage forms. The oral dosage forms may also be formulated as "controlled release" dosage forms. "Controlled," "sustained," "extended" or "time release" dosage forms are equivalent terms that describe the type of active agent delivery that occurs when the active agent is released from a delivery vehicle at an ascertainable and manipulatable rate over a period of time, which is generally on the order of minutes, hours or days, typically ranging from about sixty minutes to about 3 days, rather than being dispersed immediately upon entry into the digestive tract or upon contact with gastric fluid. A controlled release rate can vary as a function of a multiplicity of factors. Factors influencing the rate of delivery in controlled release include the particle size, composition, porosity, charge structure, and degree of hydration of the delivery vehicle and the active ingredient(s), the acidity of the environment (either internal or external to the delivery vehicle), and the solubility of the active agent in the physiological environment, i.e., the particular location along the digestive tract. Typical parameters for dissolution test of controlled release forms are found in U.S. Pharmacopeia standard <724>.

[57] The following examples illustrate the invention without limitation. All parts and percentages are given by weight unless otherwise indicated.

Example 1

Preparation of Oxycodone/Ibuprofen Tablets

[58] Ibuprofen 90% (DCI-90) (454.54 mg/tablet, equivalent to 400 mg/tablet ibuprofen), oxycodone hydrochloride (5.17 mg/tablet, equivalent to 5.00 mg/tablet oxycodone hydrochloride), and povidone USP (available as Plasdone K-30 from International Specialty Products Corporation of Wayne, NJ) (4.55 mg/tablet) were mixed for 5 minutes. The ingredients were granulated with purified water. After drying the wet granules, colloidal silicon dioxide NF (2.30 mg/tablet), microcrystalline cellulose NF (199.84 mg/tablet), and stearic acid NF (13.60 mg/tablet) were added. The blend was compressed and the tablets were coated with an aqueous coating concentrate (Colorcon Formulation No. YSI-7085 or YSI-7411, Colorcon of West Point, PA) (27.00 mg/tablet).

Example 2

[59] Ibuprofen USP 90% (DCI-90) (444.40 mg/tablet, equivalent to 400 mg/tablet ibuprofen), oxycodone hydrochloride USP (5.10 mg/tablet), and povidone USP (4.50 mg/tablet) were mixed in a high shear granulator. The ingredients were granulated with purified water and the wet mass dried using a fluid bed drier. The dried granules were milled and mixed in a twin shell blender with colloidal silicon dioxide NF (2.80 mg/tablet), sodium starch glycolate NF (22.80 mg/tablet), microcrystalline cellulose NF (40.90 mg/tablet), lactose monohydrate NF (41.40 mg/tablet), stearic acid NF (13.60 mg/tablet), and a portion of calcium stearate NF (7.50 mg/tablet) for 35 minutes. The remaining portion of calcium stearate NF was added to the blender and mixed for an additional 5 minutes. The blend was compressed using a rotary tablet press. The tablets were then coated with Opadry White (17.50 mg/tablet) with a perforated coating pan.

Example 2A

[60] Tablets were prepared according to the procedure in Example 2 without the Opadry White coating. Once all of the materials were added together, they were blended in a 10-ft^3 blender rotating at 20 rpm for 40 minutes. The blend was then compressed with a rotary tablet press. Sticking was observed almost immediately during the compression operation. After 10 minutes, tablet appearance was deemed unacceptable and the compression was discontinued.

Example 3

[61] Ibuprofen USP 90% (DCI-90) (222.22 mg/tablet, equivalent to 200 mg/tablet ibuprofen), oxycodone hydrochloride USP (5.10 mg/tablet), and povidone USP (2.25 mg/tablet) were mixed in a high shear granulator. The ingredients were granulated with purified water and the wet mass dried using a fluid bed drier. The dried granules were milled and mixed in a twin shell blender with colloidal silicon dioxide NF (1.40 mg/tablet), sodium starch glycolate NF (11.40 mg/tablet), microcrystalline cellulose NF (28.45 mg/tablet), lactose monohydrate NF (28.63 mg/tablet), stearic acid NF (6.80 mg/tablet), and a portion of the calcium stearate NF lot (3.75 mg/tablet) for 35 minutes. The remaining portion of calcium stearate was added to the blender and mixed for an additional 5 minutes. The blend was compressed by a rotary tablet press. The tablets were then coated with Opadry White (9.30 mg/tablet) with a perforated coating pan.

Example 4

[62] Ibuprofen USP 90% (DCI-90) (444.40 mg/tablet, equivalent to 400 mg/tablet ibuprofen), oxycodone hydrochloride USP (5.10 mg/tablet), and povidone USP

(4.50 mg/tablet) were mixed in a high shear granulator. The ingredients were granulated with purified water and the wet mass dried using a fluid bed drier. The dried granules were milled and mixed in a twin shell blender with colloidal silicon dioxide NF (2.80 mg/tablet), sodium starch glycolate NF (22.80 mg/tablet), microcrystalline cellulose NF (40.90 mg/tablet), lactose monohydrate NF (41.00 mg/tablet), stearic acid NF (13.60 mg/tablet), and a portion of the calcium stearate NF lot (7.50 mg/tablet) for 35 minutes. The remaining portion of calcium stearate was added to the blender and mixed for an additional 5 minutes. The blend was compressed by a rotary tablet press. The tablets were then coated with Opadry II White (17.50 mg/tablet) with a perforated coating pan.

Example 4A

[63] The procedure of Example 4 was repeated with 10.2 mg/tablet of oxycodone hydrochloride USP, 22.8 mg/tablet of sodium starch glycolate NF, and 35.8 mg/tablet microcrystalline cellulose NF.

Example 5

[64] Prosolv SMCC 90 (which is a mixture of colloidal silicon dioxide NF and microcrystalline cellulose NF available from Penwest Pharmaceuticals Co. of Patterson, NJ) (104.2 mg/tablet) and oxycodone hydrochloride USP (5.0 mg/tablet) were mixed in a twin shell blender for 10 minutes. A portion (approximately 25% or 112.5 mg/tablet) of ibuprofen USP 90% (DCI-90) (total 450.0 mg/tablet) was added and mixed for 10 minutes. Stearic acid NF (13.6 mg/tablet), calcium stearate NF (4.5 mg/tablet), sodium starch glycolate NF (22.7 mg/tablet), and the remaining ibuprofen USP 90% (approximately 337.5 mg/tablet) were added to the blender and mixed for 40 minutes. The blend was compressed by a rotary

tablet press. The tablets were then coated with Opadry II White (18.0 mg/tablet) with a perforated coating pan.

Example 6

[65] The procedure of Example 5 was repeated with 10.0 mg/tablet of oxycodone hydrochloride USP and 99.2 mg/tablet of Prosolv SMCC 90.

Example 7

[66] The following two clinical studies were performed to evaluate the analgesic efficacy of a unitary formulation containing oxycodone HCl and ibuprofen.

Study 1

[67] 498 patients were randomized in a double-blind, placebo- and active-controlled, multicenter, parallel study. Patients with moderate to severe pain following surgical removal of at least 2 ipsilateral bony impacted third molars received a single dose of oxycodone HCl/ibuprofen 5/400 mg combination (as a single tablet) (prepared as described in Example 4), 5 mg oxycodone HCl, 400 mg ibuprofen, or placebo. The primary efficacy paramaters of total pain relief and sum of pain intensity difference were evaluated for 6 hours postdose.

[68] The 5 mg oxycodone HCl/400 mg ibuprofen tablet (21.4 minutes) resulted in an earlier onset of analgesia compared with 400 mg ibuprofen (29.7 minutes) ($P<0.01$) or 5 mg oxycodone HCl (> 360 minutes) ($P<0.001$). The oxycodone HCl/ibuprofen tablet had a 28% faster median time to onset of pain relief than did ibuprofen alone (21.4 v. 29.7 minutes).

Study 2

[69] In a multi-site, double-blind, parallel-group study, patients with moderate to severe pain following surgical removal of at least 2 ipsilateral bone impacted third molars were randomized to a single dose of oxycodone HCl/ibuprofen 5/400 mg (single tablet) (n=171) (prepared as described in Example 4), oxycodone HCl/ibuprofen 10/400 mg (single tablet) (prepared as described in Example 4A) (n=169), 400 mg ibuprofen (n=171), 5 mg oxycodone HCl (n=57), 10 mg oxycodone HCl (n=57), and placebo (n=57) and evaluated for 6 hours postdose. The median times to onset of pain relief for 5 mg oxycodone HCl/400 mg ibuprofen, 10 mg oxycodone HCl/400 mg ibuprofen, 400 mg ibuprofen, 5 mg oxycodone HCl, and 10 mg oxycodone HCl were 25.4, 22.5, 28.0, 67.3, and 63.4 minutes, respectively.

[70] The results from these two studies were pooled. Figures 1-3 show the pain intensity difference (PID), pain relief (PR) scores, and combined pain relief and pain intensity difference (PRID), respectively, over 6 hours for the pooled data for 5 mg oxycodone/400 mg ibuprofen, 400 mg ibuprofen, 5 mg oxycodone HCl, and placebo. In the pooled analysis, the median time to onset of pain relief for 5 mg oxycodone HCl/400 mg ibuprofen was 22.9 minutes, which was significantly ($p<0.05$) shorter than for ibuprofen alone (29.0 minutes). The median time could not be estimated for the oxycodone and placebo groups as fewer than 50% of the patients in these groups experienced pain relief.

Example 8

[71] A randomized, two-way crossover study in healthy male subjects was performed. Subjects received the following treatments in random order:

A. one tablet prepared by the procedure in Example 1 (5 mg oxycodone HCl and 400 mg ibuprofen) with 240 mL of water after overnight fast, and

B. one oxycodone tablet (5 mg) and 2 x 200 mg immediate release Medipren® ibuprofen caplets (available from Johnson & Johnson of New Brunswick, NJ) with 240 mL of water after overnight fast.

[72] There was a 7-day washout between periods.

[73] 24 male subjects were entered into the study. All the subjects completed the study. The average age of the subjects was 25 ± 5 years (range, 20-38 years).

[74] Blood samples were taken at 0.0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 7, and 10 hours after the administration of the two treatments. Blood samples were collected and plasma was analyzed for oxycodone and total ibuprofen concentrations.

[75] The average plasma concentration time profiles for ibuprofen and oxycodone are shown in Figures 4 and 5, respectively. The average C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, and $T_{1/2}$ (± standard deviation) for oxycodone and ibuprofen, based on the two one-sided test procedure using log-transformed data, are shown in Tables 1 and 2, respectively.

Table 1

Ibuprofen Profile

	Tablet of Example 1	5 mg Oxycodone Tablet with 2 x 200 mg Ibuprofen (Medipren®) Tablets
C_{max} (μg/mL)	30.6 ± 8.8 (90% C.I.*: 97-121)	28.1 ± 7.5
AUC_{0-t} (μg·hr/mL)	112.4 ± 22.2 (90% C.I.*: 96-108)	109.5 ± 16.7
$AUC_{0-\infty}$ (μg·hr/mL)	122.4 ± 28..5 (90% C.I.*: 97-113)	115.8 ± 19.8
T_{max} (hr)	1.4 ± 0.9	2.2 ± 1.5
$T_{1/2}$ (hr)	2.1 ± 0.6	1.9 ± 0.4

* - C.I. = "Confidence Interval"

Table 2

Oxycodone Profile

	Tablet of Example 1	5 mg Oxycodone Tablet with 2 x 200 mg Ibuprofen (Medipren®) Tablets
C_{max} (ng/mL)	7.5 ± 1.8 (90% C.I.: 85-102)	8.0 ± 1.7
AUC_{0-t} (ng·hr/mL)	19.4 ± 5.1 (90% C.I.: 91-110)	19.2 ± 3.6
$AUC_{0-\infty}$ (ng·hr/mL)	36.5 ± 10.7 (90% C.I.: 90-111)	36.4 ± 5.2
T_{max} (hr)	1.4 ± 0.6	1.4 ± 0.4
$T_{1/2}$ (hr)	2.8 ± 0.8	2.8 ± 0.9

Example 9

[76] The objective of this study was to investigate the effects of potential drug-drug interaction between ibuprofen and oxycodone on their permeability characteristics across Caco-2 cell monolayers. Ibuprofen/oxycodone HCl tablets containing 5 mg of oxycodone (hydrochloride salt, all mass concentrations of oxycodone used in this study were based on the total weight of the hydrochloride salt, not on its free base) and 400 mg of ibuprofen were used. The dose ratio of oxycodone to ibuprofen was 1:80 (w/w). The molecular weight of oxycodone hydrochloride is 351.87 and the molecular weight of ibuprofen is 206.28; therefore, the molar ratio of oxycodone/ibuprofen (5 mg/400 mg) is

1:136. According to the literature, the absolute bioavailability of oxycodone was reported to be 87%, and the bioavailability of ibuprofen was reported to approach 100%. Leow, K.P., Smith, M.T., Williams, B. and Cramond, T., "Single-Dose and Steady State Pharmacokinetics and Pharmacodynamics of Oxycodone in Patients with Cancer", *Clin. Pharmacol. Ther.*, 52: 487 - 495 (1992); Hall, S.D., Rudy, A.C., Knight, P.M. and Brater, D.C., "Lack of Presystemic Inversion of (R)- to (S)-Ibuprofen in Humans", *Clin. Pharmacol. Therap.*, 53: 393 - 400 (1993). Caco-2 cell monolayers have been used as a model of intestinal mucosa for predicting oral drug absorption (P. Artursson. Epithelial transport of drugs in cell culture. I: A model for studying the passive diffusion of drugs over intestinal absorptive (Caco-2) cells. *J Pharm Sci.* 79:476-482. (1990)). The transport experiments of oxycodone and ibuprofen were conducted in the apical (AP) to basolateral (BL) direction across Caco-2 cell monolayers.

Materials

[77] The Caco-2 cell monolayers were grown in the laboratory. Hank's balanced salt solution buffer (HBSS) was prepared in the laboratories.

Preparation of dosing solutions of oxycodone and ibuprofen

[78] Solutions containing 0.02 mg/ml oxycodone hydrochloride and 0, 0.8, 1.6, or 3.2 mg/ml ibuprofen were prepared as follows. One stock solution of oxycodone in DMSO (10 mg/ml, hydrochloride salt) was prepared. Two stock solutions of ibuprofen in DMSO (100 mg/ml and 200 mg/ml) were prepared. The solutions of oxycodone (0.02 mg/ml, hydrochloride salt) were made by diluting the stock solutions in HBSS (pH=6.8). A

total of 40 and 80 µl of ibuprofen DMSO stock solutions (100 mg/ml) and 80 µl of ibuprofen DMSO stock solution (200 mg/ml ibuprofen) were transferred to 5 ml of solutions of oxycodone (0.02 mg/ml), respectively. The concentrations of ibuprofen in dosing solutions were 0, 0.8, 1.6 and 3.2 mg/ml, respectively. The concentration of DMSO in all the donor and receiver solutions was adjusted to 1.6%.

[79] The solutions of ibuprofen (0.2 mg/ml) were made transferring 200 µl the ibuprofen stock solution (10 mg/ml) into 10 ml of HBSS (pH=6.8). 0, 2.5, 5, and 10 µl of the oxycodone DMSO stock solution (10 mg/ml) were transferred to 10 ml of the aforementioned solutions of ibuprofen (200 µg/ml), respectively. The concentrations of oxycodone (hydrochloride salt) in these solutions were 0, 2.5, 5, and 10 µg/ml, respectively, and the concentration of DMSO in the donor compartment was about 2%. The concentration of DMSO in the receiver solution was adjusted to 2%.

Experiment

[80] The transport experiments were performed using Caco-2 cell monolayers grown on a 12-well TRANSWELL® system (Costar, Cambridge, Mass.). All experiments were done at 37°C with constant mixing in a water shaker-bath (60 rpm). Both the AP and the BL compartments of each insert were washed twice with 37°C HBSS (pH=7.4) and incubated for 15 minutes. The pH value of HBSS was 6.8 for the donor (AP) and 7.4 for the receiver (BL) solutions. 500 µl of solution was added to the AP compartment and 1500 µl of solution was placed in the BL compartment. Aliquots (750 µl) were withdrawn from the receiver side at 20-minute time intervals to 80 minutes. HBSS was replaced in the receiver side after sampling. Aliquots (50 µl) were withdrawn from the donor

side at 10 minutes and 80 minutes. Each treatment was performed in triplicate. The membrane integrity of the cell monolayers was monitored before and after the transport experiments by measuring the transepithelial electric resistant (TEER) of the cell monolayers. Samples then underwent LC/MS/MS analysis.

[81] The transport of oxycodone (0.02 mg/ml) across Caco-2 cell monolayers in the AP-to-BL direction was measured in the absence and presence of increasing concentrations of ibuprofen (0, 0.8 mg/ml, 1.6 mg/ml, and 3.2 mg/ml). The dose ratios of oxycodone to ibuprofen were 0, 1:40, 1:80, and 1:160 (w/w), respectively.

[82] The transport of ibuprofen (0.2 mg/ml) across Caco-2 cell monolayers in the AP-to-BL direction was conducted in the absence and presence of increasing concentrations of oxycodone (0, 2.5 μg/ml, 5 μg/ml, and 10 μg/ml). The dose ratios of oxycodone to ibuprofen were 0, 1:80, 1:40, and 1:20 (w/w), respectively.

[83] Apparent permeability coefficient (P_{app}) values were calculated using the equation:

$$P_{app} = \Delta Q/\Delta t/(A*C_0) \qquad (1)$$

where $\Delta Q/\Delta t$ is the linear appearance rate of mass in the receiver solution, A is the filter/cell surface area (1 cm^2), and C_0 is the initial concentration of the test compounds.

[84] Statistical analyses were performed using Student's two-tailed *t*-test between two mean values. A probability of less than 0.05 ($p < 0.05$) was considered to be statistically significant.

Results

[85] As shown in Table 3 below and Figure 6, oxycodone had a P_{app} value of $5.42 \pm 0.09 \times 10^{-5}$ cm/s across Caco-2 cell monolayers. In the presence of 0.8 mg/ml of ibuprofen, the permeability of oxycodone was enhanced to $5.69 \pm 0.14 \times 10^{-5}$ cm/s. Ibuprofen at the concentration of 1.6 mg/ml appeared to marginally increase the permeability of oxycodone although the effects were not significant. When 3.2 mg/ml of ibuprofen was prepared in HBSS, ibuprofen formed a precipitate and slightly decreased the permeability of oxycodone to $5.05 \pm 0.05 \times 10^{-5}$ cm/s. A portion of oxycodone might be coprecipitated from the transport media and result in less amount of oxycodone available for transport, thus decreasing the overall permeability of oxycodone. The membrane integrity of Caco-2 cell monolayers was monitored before and after the transport experiments. The TEER values of cell monolayers were in the range of 980-1002 Ωcm^2 before the transport experiments and the values were not changed after the transport experiments were conducted. Therefore, ibuprofen and oxycodone at the concentrations used in the experiment did not compromise the integrity of Caco-2 cell monolayers.

Table 3

Permeability of Oxycodone across Caco-2 Cell Monolayers in the Absence and Presence of Increasing Concentrations of Ibuprofen

Concentration of ibuprofen in the transport medium (mg/ml)	Apparent permeability coefficients of oxycodone (10^{-5} cm/s) (± standard deviation) (n=3)
0	5.42 ± 0.09
0.8	5.69 ± 0.14
1.6	5.51 ± 0.13
3.2	5.05 ± 0.05

[86] Although ibuprofen only exhibited a marginal effect on the overall permeability of oxycodone over the 80-minute transport period of time, it significantly enhanced the initial transport rate of oxycodone across Caco-2 cell monolayers. As shown in Table 4 and Figure 7, after the initial 20-minute transport period of time, the percentage of transported oxycodone from apical to basolateral compartment was increased from 15% to 20% and 19% in the presence of 0.8 mg/ml and 1.6 mg/ml of ibuprofen, respectively. Ibuprofen at the concentration of 3.2 mg/ml did not increase the transport of oxycodone due to its precipitating from the transport media. Since the rate of onset of action of a drug is dependent on the time for the drug to be absorbed and accumulated to its low concentration limit of the therapeutics window, the initial absorption rate of oxycodone and ibuprofen in the GI tract might play an important role in its faster onset of action. The increased initial

transport rate of oxycodone by ibuprofen may contribute to the fast onset of action of oxycodone/ibuprofen formulation.

Table 4

Permeability of Oxycodone across Caco-2 Cell Monolayers in the Absence and Presence of Increasing Concentrations of Ibuprofen after 20 minutes

Concentration of ibuprofen in the transport medium (mg/ml)	Apparent permeability coefficients of oxycodone (10^{-5} cm/s) (± standard deviation) (n=3)
0	1.5 ± 0.09
0.8	2.0 ± 0.06
1.6	1.9 ± 0.03
3.2	1.6 ± 0.07

[87] Oxycodone is a tertiary amine molecule. Its pKa is about 9. It is highly charged at all physiological pH. At the oxycodone/ibuprofen dose ratios of 1:40 (oxycodone: 0.02 mg/ml, ibuprofen 0.8 mg/ml) and 1:80 (oxycodone: 0.02 mg/ml, ibuprofen 1.6 mg/ml), the molar ratios of oxycodone to ibuprofen in the transport buffer were 1:68 and 1:136, respectively. Each oxycodone molecule in solution had a large number of ibuprofen molecules surrounding it. Oxycodone may interact with ibuprofen, a benzeneacetic acid derivative, to form a less polar organic ion pair, thus increasing its biomembrane permeation rates.

[88] Ibuprofen has been reported to be a highly permeable drug (FDA CDER, Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/ Active Ingredients Based on a Biopharmaceutics Classification System. Food and Drug Administration: Rockville, MD, 2000. 1197-1204). As noted above, the bioavailability of ibuprofen approaches 100%. As shown in Table 5 below and Figure 8, ibuprofen had a Caco-2 permeability value of $5.65 \pm 0.43 \times 10^{-5}$ cm/s, which is consistent with its highly permeable characteristics. In the presence of oxycodone at oxycodone/ibuprofen dose ratios of 1:80, 1:40, and 1:20 (w/w), the Caco-2 permeability of ibuprofen was no different from the control (Table 5 and Figure 8). At the oxycodone/ibuprofen dose ratios of 1:80, 1:40, and 1:20 (w/w) in the transport buffer, the molar ratios of oxycodone to ibuprofen were 1:136, 1:68, and 1:34, respectively.

Table 5

Permeability of Iburpofen across Caco-2 Cell Monolayers in the Absence and Presence of Increasing Concentrations of Oxycodone

Concentration of oxycodone in the transport medium (μg/ml)	Apparent permeability coefficients of ibuprofen (10^{-5} cm/s) (± standard deviation) (n=3)
0	5.65 ± 0.43
2.5	5.27 ± 0.39
5	5.43 ± 0.11
10	6.15 ± 0.18

[89] In conclusion, ibuprofen increased the initial transport rates of oxycodone across Caco-2 cell monolayers. The fast accumulation of oxycodone in patients may result in a faster onset of action on pain relief.

Example 10

[90] The dissolution and Caco-2 cell monolayer permeation characteristics of ibuprofen and oxycodone from unitary tablets containing 400 mg ibuprofen and 5 mg of oxycodone hydrochloride as prepared in Example 4 (hereafter referred to as the "5/400 unitary tablets"), tablets containing 200 mg of ibuprofen (Nuprin® tablets), and tablets containing 5 mg oxycodone hydrochloride (Roxicodone™ tablets) were compared in the continuous dissolution/Caco-2 cell monolayer system shown in Figure 9. The continuous dissolution/Caco-2 system includes a Vankel dissolution apparatus (I or II) (available from Varian, Inc. of Cary, NC) and a side-by-side diffusion cell. In this system, dissolution and permeation of a drug across Caco-2 cell monolayers occurs continuously. Therefore, monitoring of accumulative of drug appearing in the receiver side of Caco-2 cell monolayers may be predictive of oral drug absorption of a dosage form.

Experimental

[91] Caco-2 cell monolayers were grown in the laboratory. Fasted state simulated small intestinal fluid (FaSSIF) buffer and Hank's balanced salt solution buffer (HBSS) were prepared in the laboratory as described in J. B. Dressman, G. L. Amidon, C. Reppas and V. P. Shah, "Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms", *Pharm Res.* **15**:11-22 (1998); and F. Tang and R. T. Borchardt, "Characterization of the efflux transporter(s) responsible for restricting intestinal

mucosa permeation of a coumarinic acid-based cyclic prodrug of the opioid peptide DADLE", *Pharm. Res.* **19**:787-793 (2002).

[92] FaSSIF buffer has been used as the bio-relevant buffer to predict the *in vivo* performance of an orally administered dosage form (J. B. Dressman, G. L. Amidon, C. Reppas and V. P. Shah, "Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms", *Pharm Res.* **15**:11-22 (1998)). FaSSIF buffer was also found to be compatible with Caco-2 cell monolayers (F. Ingels, S. Deferme, E. Destexhe, M. Oth, G. Van den Mooter and P. Augustijns. Simulated intestinal fluid as transport medium in the Caco-2 cell culture model. *Int J Pharm.* **232**:183-192 (2002)). Therefore, the dissolution studies were conducted in FaSSIF buffer in a USP apparatus II (50 rpm, 37 °C). As shown in Figure 9, in each dissolution vessel, one 5/400 unitary tablet, two Nuprin® tablets (200 mg ibuprofen per tablet, available from Bristol-Myers Squibb Co. of New York, NY), one Roxicodone™ tablet (available from Roxane Laboratories, Inc. of Columbus, OH) , or the combination of two Nuprin® tablets and one Roxicodone™ tablet was dissolved in 500 ml of FaSSIF buffer in USP apparatus I (100 rpm) at 37 °C, respectively. The dissolution medium was filtered through a 10 μm dissolution filter and transferred via a peristaltic pump to the donor compartment of the side-by-side diffusion cell. Mounted between the donor and receiver compartments of the diffusion cell was a Caco-2 cell monolayer, which was grown onto a polycarbonate Snapwell® filter (available from Costar of Cambridge, Mass.) and cultured for 21-28 days. During the dissolution-permeation study, the dissolution medium was continuously recirculated from the donor compartment back to the dissolution vessel, therefore, the drug concentration in the donor compartment of the side-by-side diffusion cell was simultaneously changing as that in the dissolution buffer. The volume of media in the

donor compartment of the side-by-side diffusion cell was maintained at 7 ml. The receiver compartment of the side-by-side diffusion cell was filled with 7 ml of HBSS. Aliquots (5 ml) were taken from the dissolution media at 5, 10, 15, 20, 30, 40, 50, and 60 minutes. 4 ml of HBSS were taken from the receiver side of the diffusion cell at 8, 13, 18, 23, 33, 43, 53, and 63 minutes taking into consideration that it took about 3 minutes to circulate drug from the dissolution vessel to the Caco-2 cell monolayer surface. 4 ml pre-warmed 37 °C-HBSS was replaced back to the receiver compartment. Samples were analyzed using HPLC or LC/MS. The low limit of quantification (LLQ) was 5 ng/ml for oxycodone LC/MS analysis. Drug concentrations below LLQ were considered as 0 ng/ml in the calculations.

Mathematical Model

[93] In a sink condition, the drug concentration in dissolution buffer can be calculated using simplified Noyes-Whitney equation 2

$$dC/dt = K \times Cs \qquad (2)$$

where K is the apparent dissolution rate constant for a formulation and Cs is the solubility of the drug substance in the dissolution buffer.

[94] Therefore, the concentration of drug at time t (Ct) can be calculated according to equation 3.

$$Ct = K \times Cs \times t \qquad (3)$$

[95] Drug permeability across the Caco-2 monolayer is calculated using modified Fick's First Law, equation 4

$$dM/dt = Papp \times A \times Ct \qquad (4)$$

where dM/dt is the rate of amount drug appearing in the receiver side, Papp is the apparent drug permeability constant across Caco-2 cell monolayers, A is the surface area of Caco-2 cell monolayer, which is 1 cm^2 for Snapwell® system, and Ct is the drug concentration in the donor compartment, which is equal to the concentration in the dissolution buffer, and is calculated in equation 2.

[96] Equation 3 is substituted into equation 4 to yield,

$$dM/dt = Papp \times A \times K \times Cs \times t \qquad (5)$$

[97] Integration of equation 5 yields

$$Mt = \tfrac{1}{2} \times Papp \times A \times K \times Cs \times t^2 \qquad (6)$$

where Mt is the accumulative amount of drug in the receiver side of the side-by-side diffusion cell. Mt integrates the contributions of dissolution and permeation processes into overall drug absorption kinetics. Therefore, monitoring of Mt may be predictive of oral drug absorption of a dosage form.

[98] Statistical analyses were performed using Student's two-tailed *t*-test between two mean values. A probability of less than 0.05 ($p < 0.05$) was considered to be statistically significant.

Results

[99] Figure 10 shows the dissolution rates of ibuprofen from the 5/400 unitary tablets, Nuprin® tablets, and the combination of Nuprin® and Roxicodone™ tablets. All formulations had rapid ibuprofen dissolution rates in the FaSSIF buffer, i.e., more than 80% of ibuprofen was dissolved in 20 minutes. The dissolved ibuprofen into dissolution buffer from all formulations approached 100% at the later time points of 40, 50, and 60

minutes. The absorption data (Figure 11) for ibuprofen in the dissolution/Caco-2 cell monolayer system were consistent with the dissolution results. As shown in Figure 11, the accumulative amounts of absorbed ibuprofen in the receiver side of the Caco-2 diffusion system were similar among the three treatments.

[100] Dissolution rates of oxycodone from the 5/400 unitary tablets, the Roxicodone™ tablets, and the combination of Nuprin® and Roxicodone™ tablets were rapid. As shown in Figure 12, more than 90% of the oxycodone was dissolved within 30 minutes for all three treatments. The dissolution rates of oxycodone from the 5/400 unitary tablets were extremely fast, i.e., 100% of oxycodone was dissolved in 15 minutes. The amounts of oxycodone dissolved from the 5/400 unitary tablets were greater than the amounts of oxycodone from Roxicodone™ tablets and the combination of Nuprin® and Roxicodone™ tablets at 10, 15, and 20 minutes (Figure 12). Figure 13 shows the accumulative amount of oxycodone in the receiver side of the Caco-2 system. The accumulative amounts of absorbed oxycodone from the 5/400 unitary tablets exhibited a trend of greater accumulation than from the other two treatments (Figure 13). The accumulative amount of oxycodone appearing in the receiver compartment of Caco-2 system for the treatment of the combination of Nuprin® and Roxicodone™ was less than the accumulative amounts of oxycodone for the 5/400 unitary tablets and Roxicodone™ treatments at the time points of 30, 40, 50, and 60 minutes (Figure 13). As discussed in the Mathematical Model section, the accumulative amount (Mt) of drug in the receiver side of dissolution/Caco-2 cell monolayer system is predictive of the oral drug absorption of a dosage form. Therefore, the aforementioned data may be indicative of the faster oral absorption of oxycodone from the 5/400 unitary tablets than the combination of Nuprin® and Roxicodone™ tablets. Since oxycodone was included in the 5/400 unitary tablets formulation to improve the anti-pain effects of ibuprofen, the faster absorption rate of

oxycodone may result in the faster onset of action of 5/400 unitary tablets than the combination of Nuprin® and Roxicodone™.

[101] The faster dissolution rate and greater amount of absorbed oxycodone from the 5/400 unitary tablets in the dissolution/Caco-2 cell monolayer system suggests rapid oral absorption of oxycodone from the 5/400 unitary tablets might be the potential reason for the fast onset of action of this drug formulation.

[102] All references cited herein are incorporated by reference. To the extent that a conflict may exist between the specification and the reference the language of the disclosure made herein controls.

What is claimed is:

1. A method of treating acute pain in a patient in need thereof comprising orally administering an effective amount of oxycodone and ibuprofen in one oral dosage form at least once a day to provide partial or complete pain relief within 30 minutes, wherein the dosage form comprises a first member selected from the group consisting of oxycodone and pharmaceutically acceptable salts thereof and a second member selected from the group consisting of ibuprofen and pharmaceutically acceptable salts thereof at a weight ratio within the range of about 1:20 to about 1:100, based on the weights of molar equivalents of oxycodone hydrochloride and ibuprofen, respectively.

2. The method of claim 1, wherein the acute pain is acute postoperative pain.

3. The method of claim 1, wherein the oral dosage form comprises about 5 mg of oxycodone or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of oxycodone hydrochloride, and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of the free acid of ibuprofen.

4. The method of claim 3, wherein the oral dosage form is a tablet or capsule.

5. The method of claim 1, wherein the oral dosage form comprises about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of oxycodone hydrochloride, and about 400 mg of ibuprofen or a

pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of the free acid of ibuprofen.

6. The method of claim 3, wherein the oral dosage form is a tablet or capsule.

7. A method of treating acute pain in a patient in need thereof comprising orally administering an oral dosage form comprising from about 5 to about 10 mg of oxycodone or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of oxycodone hydrochloride, and from about 350 to about 500 mg of ibuprofen or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of the free acid of ibuprofen.

8. The method of claim 7, wherein the oral dosage form comprises about 5 mg of oxycodone or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of oxycodone hydrochloride, and about 400 mg of ibuprofen or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of the free acid of ibuprofen.

9. The method of claim 1, wherein at least 95% by weight of the oxycodone and pharmaceutically acceptable salts thereof is released from the oral dosage form after 15 minutes in fasted state simulated intestinal fluid.

10. The method of claim 1, wherein the maxium plasma concentration of ibuprofen is reached within 1.5 hours after oral administration of the oral dosage form.

11. A method for accelerating onset of pain relief in acute postoperative pain experienced by a patient post-anesthesia comprising administering to the patient an oral dosage form comprising (a) ibuprofen or a pharmaceutically acceptable salt thereof and (b) oxycodone or a pharmaceutically acceptable salt thereof, at a weight ratio within the range of 20:1 to 100:1, based on the weights of molar equivalents of oxycodone hydrochloride and ibuprofen, respectively, wherein the amount of oxycodone or pharmaceutically acceptable salt thereof in said dosage form is within the range of about 5 and about 10 mg, based on the weight of a molar equivalent of oxycodone hydrochloride.

12. A unitary dosage form comprising:

(a) oxycodone or a pharmaceutically acceptable salt thereof;

(b) ibuprofen or a pharmaceutically acceptable salt thereof, and

(c) silicified microcrystalline cellulose.

13. The directly compressed unitary dosage form of claim 12, comprising:

(a) from about 0.7 to about 1.7% by weight of oxycodone or a pharmaceutically acceptable salt thereof, based on the weight of a molar equivalent of oxycodone hydrochloride;

(b) from about 64 to about 77% by weight of ibuprofen or a pharmaceutically acceptable salt thereof based on the weight of a molar equivalent of the free acid of ibuprofen; and

(c) from about 15 to about 22% by weight of silicified microcrystalline cellulose,

based upon 100% total weight of the directly compressed unitary dosage form.

14. The tablet of claim 13, wherein the tablet has a hardness of 12-18 kp.

Figure 1. Analysis of Pain Intensity Difference (PID) Scores Over Time

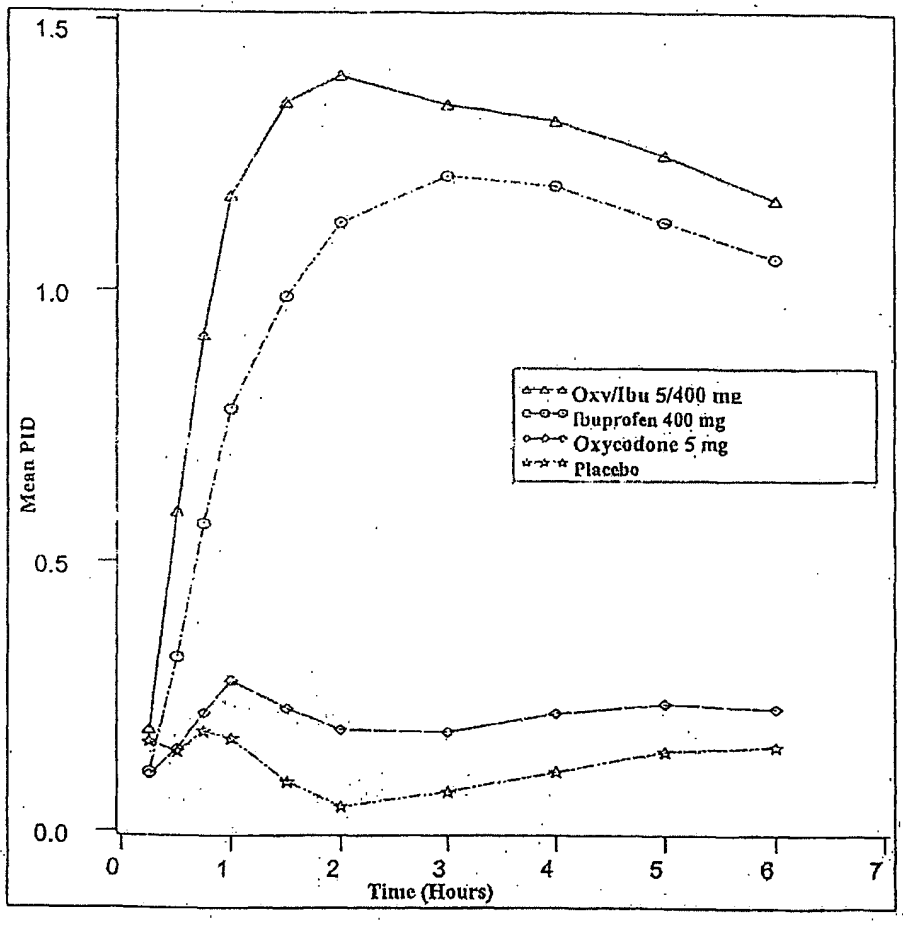


Figure 2. Analysis of Pain Relief (PR) Scores over Time

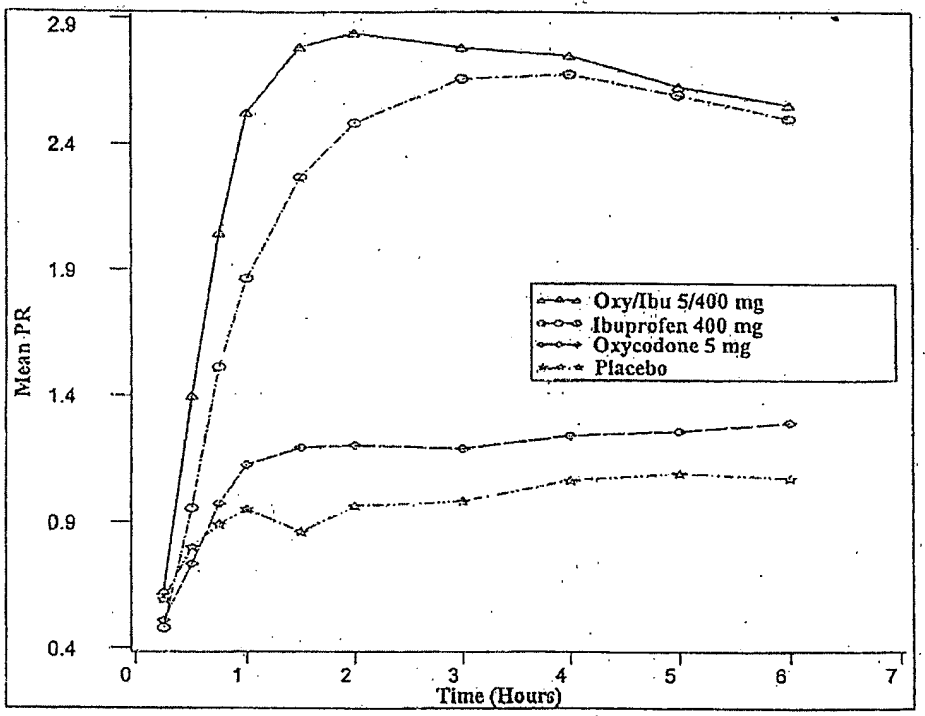
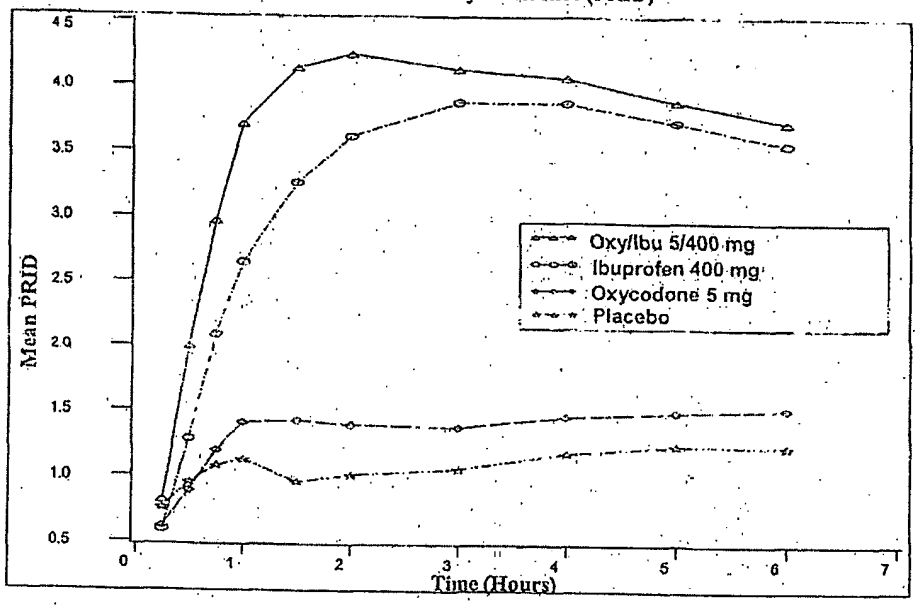


Figure 3. Pooled Efficacy Results on Combined Pain Relief and Pain Intensity Difference (PRID)



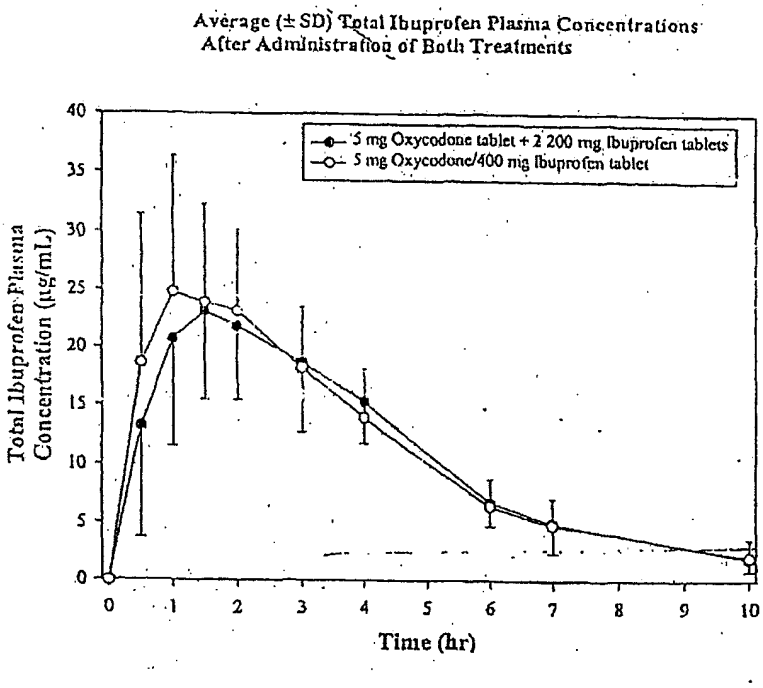

Average (± SD) Total Ibuprofen Plasma Concentrations
After Administration of Both Treatments
5 mg Oxycodone tablet + 2 200 mg Ibuprofen tablets
5 mg Oxycodone/400 mg Ibuprofen tablet
Total Ibuprofen Plasma Concentration (µg/mL)
Time (hr)
0
5
10
15
20
25
30
35
40
0
1
2
3
4
5
6
7
8
9
10

Figure 4

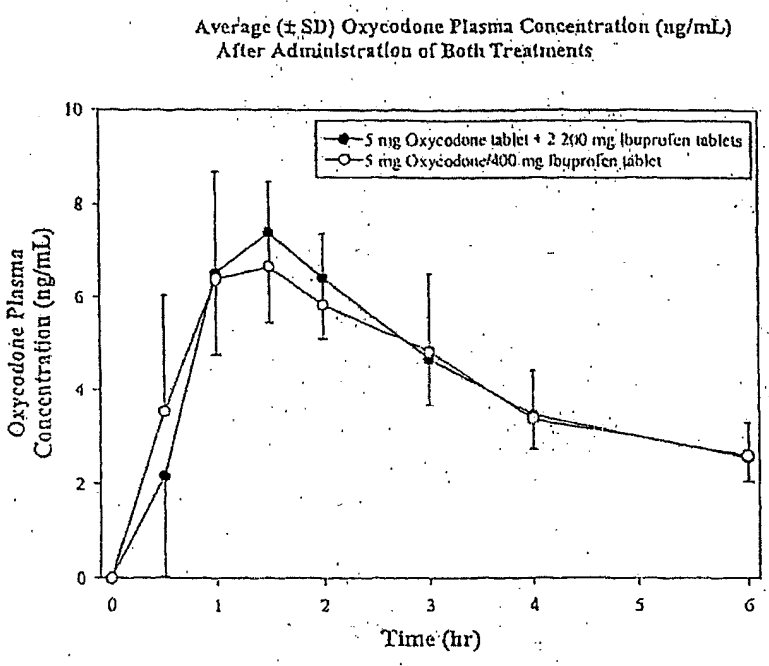
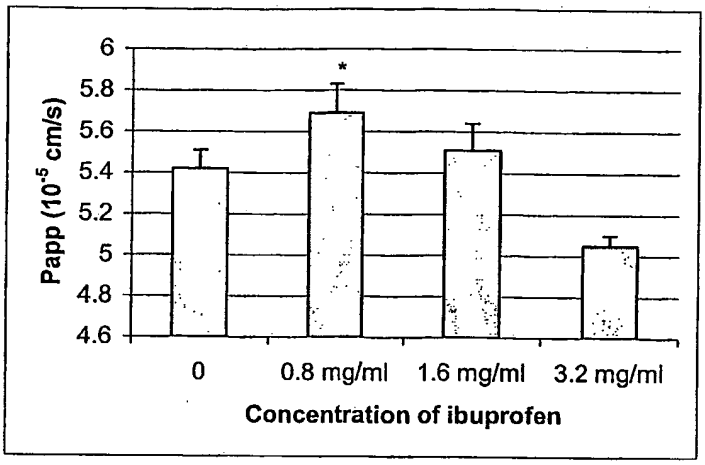

Average (± SD) Oxycodone Plasma Concentration (ng/mL)
After Administration of Both Treatments
5 mg Oxycodone tablet + 2 200 mg Ibuprofen tablets
5 mg Oxycodone/400 mg Ibuprofen tablet
Oxycodone Plasma Concentration (ng/mL)
Time (hr)
0
2
4
6
8
10
0
1
2
3
4
5
6

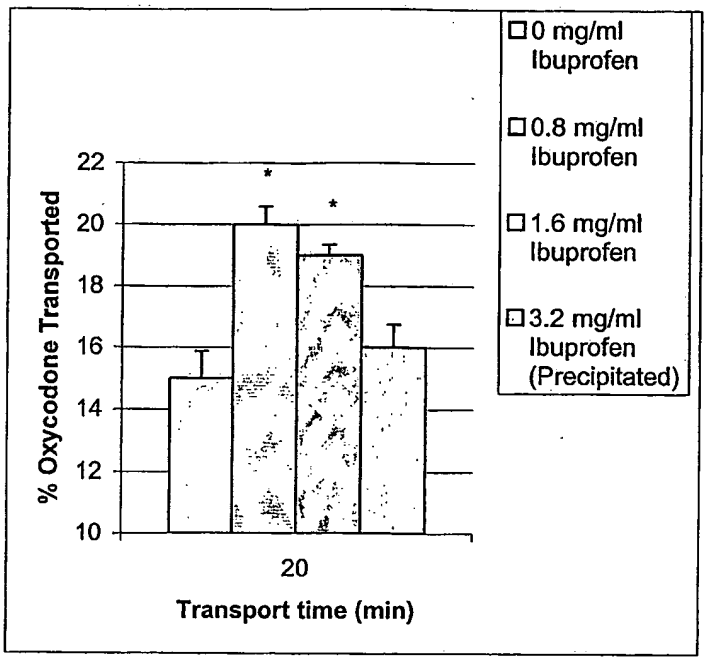
Figure 5



Effects of increasing concentrations of ibuprofen on the permeability of oxycodone across Caco-2 cell monolayers.

* - Significance level: $p < 0.05$, when compared with the permeability value in the absence of ibuprofen.

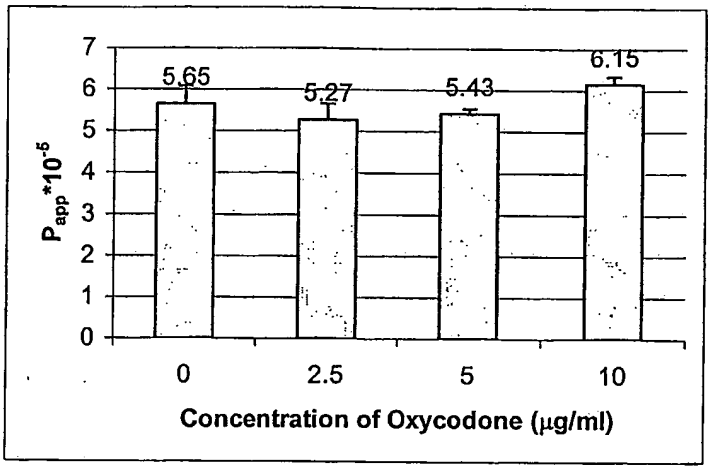
Figure 6



Effects of increasing concentrations of ibuprofen on the amount of oxycodone transported across Caco-2 cell monolayers after the initial 20 minute-transport period of time.

* - Significance level: $p < 0.05$, when compared with the value in the absence of ibuprofen.

Figure 7



Effects of increasing concentrations of oxycodone on the permeability of ibuprofen across Caco-2 cell monolayers.

Figure 8

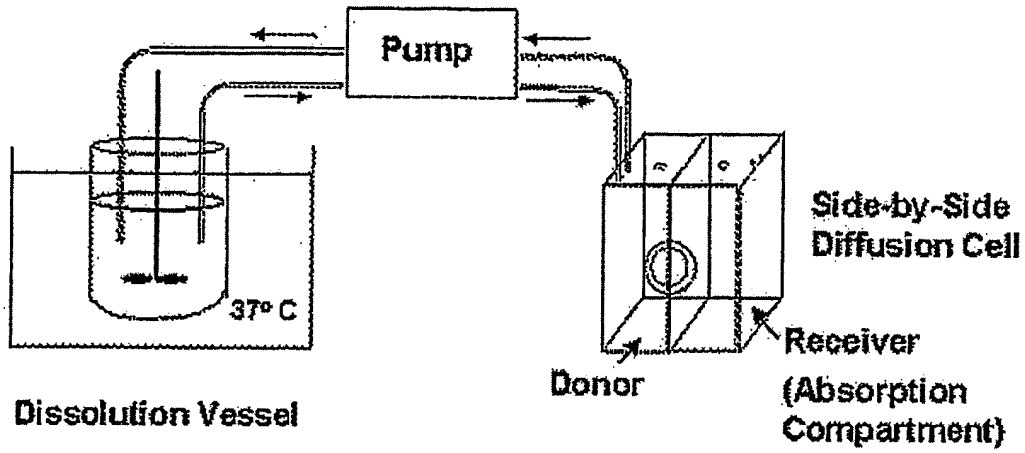
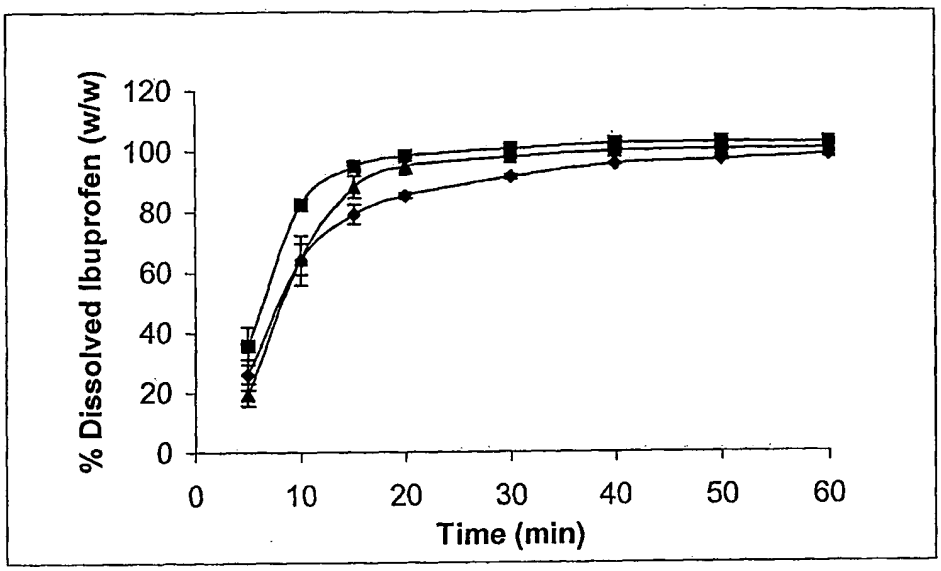

Pump
37° C
Dissolution Vessel
Side-by-Side
Diffusion Cell
Donor
Receiver
(Absorption
Compartment)

Figure 9

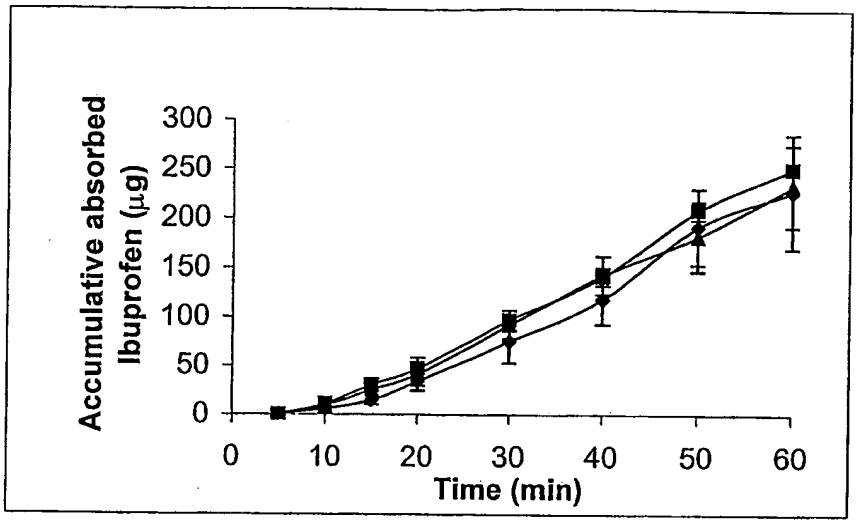


♦: One tablet of 5 mg oxycodone hydrochloride/400 mg ibuprofen

■: Two tablets of Nuprin® (200 mg ibuprofen per tablet)

▲: Two tablets of Nuprin® (200 mg ibuprofen per tablet) +
one tablet of Roxicodone™ (5 mg oxycodone hydrochloride).

Figure 10

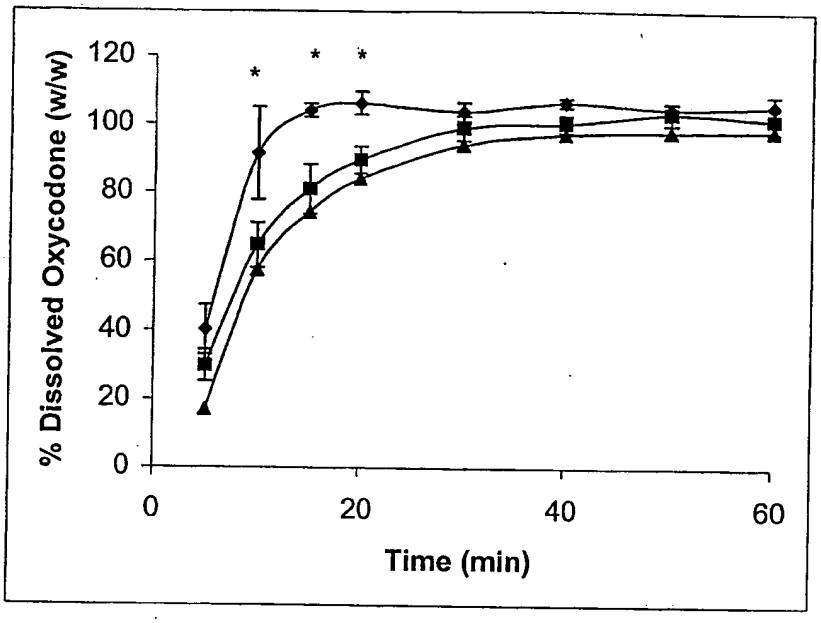


♦: One tablet of 5 mg oxycodone hydrochloride/400 mg ibuprofen

■: Two tablets of Nuprin® (200 mg ibuprofen per tablet)

▲: Two tablets of Nuprin® (200 mg ibuprofen per tablet) +
one tablet of Roxicodone™ (5 mg oxycodone hydrochloride).

Figure 11

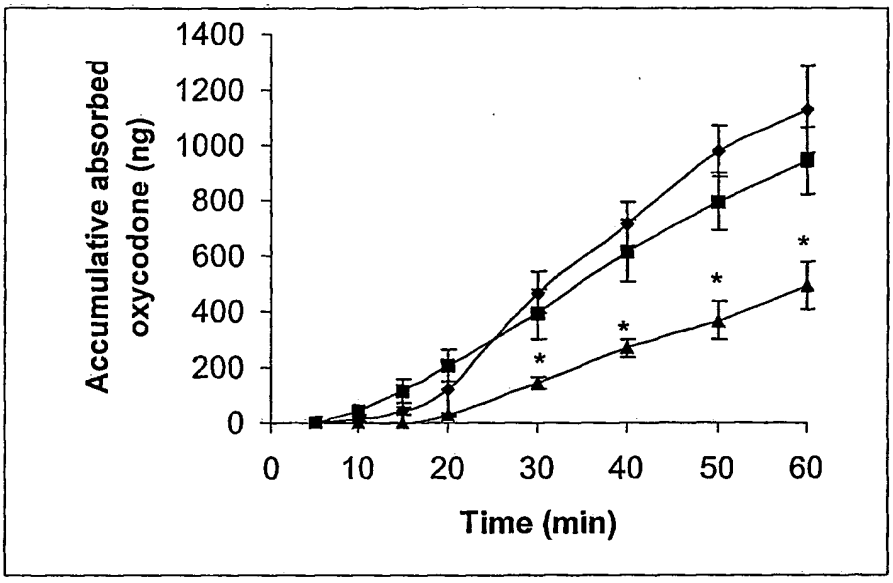


♦: One tablet of 5 mg oxycodone hydrochloride/400 mg ibuprofen

■: One tablet of Roxicodone™ (5 mg oxycodone hydrochloride)

▲: Two tablets of Nuprin® (200 mg ibuprofen per tablet) +
one tablet of Roxicodone™ (5 mg oxycodone hydrochloride).

Figure 12



♦: One tablet of 5 mg oxycodone hydrochloride/400 mg ibuprofen

■: One tablet of Roxicodone™ (5 mg oxycodone hydrochloride)

▲: Two tablets of Nuprin® (200 mg ibuprofen per tablet) +
one tablet of Roxicodone™ (5 mg oxycodone hydrochloride).

Figure 13

03269/200M292-WO

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JAY P. LEESLER
DARBY & DARBY P.C.
P.O. BOX 5257
NEW YORK, NY 10150-5257

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 200M292-WOO	Date of Mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US03/38088	International filing date *(day/month/year)* 26 November 2003 (26.11.2003)
Applicant FOREST LABORATORIES, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Shengjun Wang Telephone No. (571) 272-1600

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JAY P. LEESLER
DARBY & DARBY P.C.
P.O. BOX 5257
NEW YORK, NY 10150-5257

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing (*day/month/year*) 21 OCT 2004
Applicant's or agent's file reference 200M292-WOO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US03/38088	International filing date (*day/month/year*) 26 November 2003 (26.11.2003)
Applicant FOREST LABORATORIES, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Shengjun Wang Telephone No. (571) 272-1600

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 200M292-WOO	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/38088	International filing date (*day/month/year*) 26 November 2003 (26.11.2003)	(Earliest) Priority Date (*day/month/year*) 29 November 2002 (29.11.2002)
Applicant FOREST LABORATORIES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

Please See Continuation Sheet

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/38088

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/44, 31/19
US CL : 514/282, 570

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/282, 570

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,569,937 A (BAKER et al.) 11 February 1986 (11.02.1986) the entire documents, particularly, example 1-6, table 1 and the claims.	1, 11, --- 2-10, 12-14
Y	US 4,464,376 A (SUNSHINE et al) 07 August 1984 (07.08.1984), the entire documents, particularly, claims 18-25.	1-14
Y	EP 0 068 838 A1 (THE UPJOHN COMPANY) 05 January 1983 (05.01.1983), see the entire document	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
30 September 2004 (30.09.2004)

Date of mailing of the international search report
21 OCT 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Shengjun Wang

Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US03/38088

Continuation of Item 4 of the first sheet:
The title is too long, PCT Rule 4.3. New Title:

"Combination of Ibuprofen and Oxycodone for Acute pain Relief "

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE MEDLINE BIOSIS, search terms: oxycodone, ibuprofen, combination, synergistic, analgesic, pain, acute pain

United States Patent [19]

Baker et al.

[11] **Patent Number: 4,569,937**

[45] **Date of Patent: Feb. 11, 1986**

[54] **ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN**

[75] Inventors: **Geraldine L. Baker, Minneapolis, Minn.; William K. Schmidt, Wilmington, Del.**

[73] Assignee: **E. I. Du Pont de Nemours and Company, Wilmington, Del.**

[21] Appl. No.: **700,654**

[22] Filed: **Feb. 11, 1985**

[51] Int. Cl.[4] **A61K 31/19; A61K 31/44**

[52] U.S. Cl. **514/282; 514/557**

[58] Field of Search 424/260

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,322,427 3/1982 Buyniski et al. .

4,489,080 12/1984 Loman 424/260

FOREIGN PATENT DOCUMENTS

0068838 1/1983 European Pat. Off. .

OTHER PUBLICATIONS

S. A. Cooper et al., "Relative Efficacy of an Ibuprofen–Codeine Combination", Clin. Pharmacol. Ther., 27(2), 1980, p. 249.

AMA Drug Evaluations, Fifth Ed., 1983 Chapter 4, pp. 101–102.

Pharmacotherapy, 2, No. 3, May/Jun. 1982, Cooper et al.: Analgesic Efficacy of an Ibuprofen–Codeine Combination, pp. 162–167.

Clinical Pharmacology, K. L. Melmon, M.D., et al., Chap. 11, pp. 498–499, (1972).

The Pharmacological Basis of Therapeutics, L. S. Goodman et al., 5th Ed., Chap. 17, pp. 348–349, (1975).

Primary Examiner—Stanley J. Friedman

[57] **ABSTRACT**

Pharmaceutical compositions of narcotic analgesics and ibuprofen have been found to exhibit unexpectedly enhanced analgesic activity by applying an analysis model which considers data characterizing the analgesic effect of both the pure components as well as the fixed dose ratio combinations. This synergism enables the use of lower doses of either or both drugs with a concomitant reduction in risk of possible side effects.

6 Claims, 1 Drawing Figure

United States Patent [19]

Sunshine et al.

[11] **Patent Number: 4,464,376**

[45] **Date of Patent: Aug. 7, 1984**

[54] **ANALGESIC AND ANTI-INFLAMMATORY COMPOSITIONS COMPRISING CAFFEINE AND METHODS OF USING SAME**

[75] Inventors: **Abraham Sunshine**, New York; **Eugene M. Laska**, Larchmont; **Carole E. Siegel**, Mamaroneck, all of N.Y.

[73] Assignee: **Richardson-Vicks, Inc.**, Wilton, Conn.

[21] Appl. No.: **541,010**

[22] Filed: **Oct. 11, 1983**

Related U.S. Application Data

[63] Continuation of Ser. No. 400,597, Jul. 22, 1982, abandoned.

[51] Int. Cl.³ **A61K 31/19**; A61K 31/22; A61K 31/44; A61K 31/46; A61K 31/52; A61K 31/135; A61K 31/485

[52] U.S. Cl. **424/253**; 424/260; 424/263; 424/265; 424/311; 424/317; 424/330

[58] Field of Search 424/317, 253, 260, 263, 424/265, 311, 330

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,404,210 9/1983 Schmidt 424/260

OTHER PUBLICATIONS

Chem. Abst., 96-149, 162u (1982).

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] **ABSTRACT**

Novel analgesic and anti-inflammatory compositions of matter for use in eliciting an analgesic or anti-inflammatory response, said compositions comprising caffeine together with a selected non-narcotic analgesic/non-steroidal anti-inflammatory drug or a selected narcotic analgesic, or both, are disclosed. When used in combination with the selected drugs, caffeine enhances the analgesic or anti-inflammatory response and also hastens its onset.

25 Claims, No Drawings

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 068 838**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 82303318.8

(22) Date of filing: 25.06.82

(51) Int. Cl.³: A 61 K 31/485
//
(A61K31/485, 31/19),(A61K31/485, 31/215)

(30) Priority: 26.06.81 US 277557
26.06.81 US 277558

(43) Date of publication of application: 05.01.83
Bulletin 83/1

(84) Designated Contracting States: BE CH DE FR GB IT LI NL SE

(71) Applicant: THE UPJOHN COMPANY, 301 Henrietta Street, Kalamazoo, Michigan 49001 (US)

(72) Inventor: Lomen, Pavel Luboslav, c/o The Upjohn Company 301 Henrietta Street, Kalamazoo Michigan 49001 (US)

(74) Representative: Perry, Robert Edward et al, GILL JENNINGS & EVERY 53-64 Chancery Lane, London WC2A 1HN (GB)

(54) **Analgesic process and composition.**

(57) A process for the management of pain comprises the administration of a narcotic analgesic and ibuprofen or flurbiprofen, or a salt or ester thereof. The active ingredients may be combined in a single composition.

EP 0 068 838 A1

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 068 838**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 82303318.8

(22) Date of filing: 25.06.82

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//
(A61K31/485, 31/19),(A61K31/485, 31/215)

(30) Priority: 26.06.81 US 277557
26.06.81 US 277558

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(54) Analgesic process and composition.

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EP 0 068 838 A1

The Upjohn Company

GJE 6182/60

ANALGESIC PROCESS AND COMPOSITION

This invention relates to a process and a composition for the management of pain by the administration of narcotic analgesics.

Narcotic analgesics have been used for the relief of moderate to severe pain. Severe pain, particularly, has required the use of narcotic analgesics in large and increasing dosage amounts.

A disadvantage of the narcotic analgesics is the development of dependence or addiction and tolerance to their action. Further, adverse reactions, including respiratory and circulatory depression, are observed when large doses are used.

Ibuprofen and flurbiprofen are non-steroidal anti-inflammatory drugs. They have been used in rheumatic and degenerative diseases of the joints, for reducing platelet adhesiveness, and for dental pain.

It has now been found that, when separately or simultaneously administered to a subject, a narcotic analgesic and ibuprofen or flurbiprofen, or a salt or ester thereof, can act synergically in the management of severe to moderate pain.

Narcotic analgesics are, in general, well known. Suitable such compounds for use in the present invention are the naturally-occurring opium alkaloids and their semi-synthetic and synthetic derivatives. Examples are morphine, hydromorphone, oxymorphone, levorphanol, methadone, meperidine, anileridine, alphaprodine, fentanol, codeine, codone, and oxycodone.

The narcotic analgesics are used together with ibuprofen (p-isobutylhydratopic acid) or flurbiprofen (3-fluoro-4-phenylhydratropic acid) or a pharmacologically acceptable salt or ester thereof. Suitable salts are the alkali metal, alkaline earth and ammonium salts. Suitable esters are the C_{1-8} alkyl esters, including the isomeric forms thereof.

It can be that utilisation of the in-

vention results in better control of pain while delaying or eliminating narcotic dependance and resistance.

The dosage amount initially is the usual dosage amount for the narcotic analgesic and about 50 mg of ibuprofen four or five times a day. After two days of administering the combination, the dose amount of narcotic analgesic is gradually lowered over a period of fourteen days to the lowest acceptable amount of narcotic to maintain analgesia from the combination. After fourteen days when the lowest narcotic amount is determined, the amount of ibuprofen is lowered to 100-200 mg/day to maintain the same control of pain.

For flurbiprofen the dosage amount initially is the usual dosage amount for the narcotic analgesic and about 50 mg of flurbiprofen four or five times a day. After two days of administering the combination, the dose amount of narcotic analgesic is gradually lowered over a period of fourteen days to the lowest acceptable amount of narcotic to maintain analgesia from the combination. After fourteen days when the lowest narcotic amount is determined, the amount of flurbiprofen is lowered to 100-200 mg/day to maintain the same control of pain.

The narcotic analgesic and ibuprofen or flurbiprofen can be administered in the same dosage unit or can be prepared in separate dosage units and the dosage units administered at the same time. Different forms of dosage units can be used, i.e., a tablet of ibuprofen or flurbiprofen and an injection of narcotic.

The compositions of the present invention are preferably presented for systemic administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile nonparenteral solutions or suspensions, and oral solutions or suspensions and the like, containing suitable quantities of the synergistic combination of active ingredients.

For oral administration either solid or fluid unit dosage forms can be prepared.

Powders are prepared quite simply by comminuting the active ingredients to a suitably fine size and mixing with a similarly comminuted diluent. The diluent can be an edible carbohydrate material such as lactose or starch. Advantageously, a sweetening agent or sugar is present as well as a flavoring oil.

Capsules are produced by preparing a powder mixture and filling

into formed gelatin sheaths. Advantageously, as an adjuvant to the filling operation, lubricant such as talc magnesium stearate, calcium stearate and the like is added to the powder mixture before the filling operation.

Soft gelatin capsules are prepared by machine encapsulation of a slurry of active ingredients with an acceptable vegetable oil, light liquid petrolatum or other inert oil or triglyceride.

Tablets are made by preparing a powder mixture, granulating or slugging, adding a lubricant and pressing into tablets. The powder mixture is prepared by mixing the active ingredients, suitably comminutd, with a diluent or base such as starch lactose, kaolin, dicalcium phosphate and the like. The powder mixture can be granulated by wetting with a binder such as corn syrup, gelating solution, methylcellulose solution or acacia mucilage and forcing through a screen. As an alternative to granulating, the powder mixture can be slugged, i.e., run through the tablet machine and the resulting imperfectly formed tablets broken into pieces (slugs). The slugs can be lubricated to prevent sticking to the tablet-forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets.

Advantageously, the tablet can be provided with a protective coating consisting of a sealing coat or enteric coat of shellac, a coating of sugar and methylcellulose and a polish coating of carnauba wax.

Fluid unit dosage forms for oral administration such as syrups, elixirs and suspensions can be prepared wherein each teaspoonful of composition contains a predetermined amount of the active ingredients for administration. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic vehicle with suitable sweeteners together with a flavoring agent. Suspensions can be prepared of the insoluble forms with a suitable vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

For parenteral administration, fluid unit dosage forms are prepared utilizing the active ingredients and a sterile vehicle, water being preferred. The active ingredients, depending on the form and concentration used, can be either suspended or dissolved in the ve-

hicle. In preparing solutions, the water-soluble active ingredients can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampule and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. Cosolvents such as ethanol or propylene glycol can be used in the solvent system. Parenteral suspensions are prepared in substantially the same manner except that the active ingredients are suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The active ingredients can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active ingredients.

In addition to oral and parenteral administration, the rectal and vaginal routes can be utilized. Active ingredients can be administered by means of a suppository. A vehicle which has a melting point at about body temperature or one that is readily soluble can be utilized. For example, cocoa butter and various polyethylene glycols (carbowaxes) can serve as the vehicle.

The term "unit dosage form" as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specification for the novel unit dosage forms of this invention are dictated by and are directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitation inherent in the art of compounding such an active material for therapeutic use in humans, as disclosed in this specification, these being features of the present invention. Examples of suitable unit dosages forms in accord with this invention are tablets, capsules, troches, suppositories, powder packets, wafers, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing and other forms as herein described.

The following examples are illustrative of the present invention, but are not intended to be limiting.

Example 1 Hard Gelatin Capsules

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 50 mg of ibuprofen and 15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

Ibuprofen	50 gm
Morphine sulfate	15 gm
Lactose	100 gm
Corn starch	20 gm
Talc	20 gm
Magnesium stearate	2 gm

The ibuprofen and morphine sulfate finely divided by means of an air micronizer, are added to the other finely powdered ingredients, mixed thoroughly and then encapsulated in the usual manner.

The foregoing capsules are useful for preventing pain following laparotomy by the oral administration of one capsule four times a day.

Using the procedure above, capsules are similarly prepared containing morphine sulfate in 7.5 and 3.75 mg amounts by substituting 7.5 and 3.75 gm of morphine sulfate for the 15 gm used above. These capsules are used to reduce the narcotic dose of the preceeding examples.

Example 2 Soft Gelatin Capsules

One piece soft gelatin capsules for oral use, each containing 50 mg of ibuprofen and 15 mg of morphine sulfate (finely divided by means of an air micronizer) are prepared by first suspending the compounds in 0.5 ml of corn oil to render the material capsulatable and then capsulating in the above manner.

The foregoing capsules are useful for preventing pain following caesarian section by the oral administratin of one capsule four times a day.

Example 3 Tablets

One thousand tablets, each containing 50 mg of ibuprofen and 15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

Ibuprofen micronized	50 gm
Morphine sulfate	15 gm
Lactose	75 gm
Corn starch	50 gm
Magnesium stearate	4 gm
Light liquid petrolatum	5 gm

The ibuprofen and morphine sulfate (finely divided by means of an air micronizer) are added to the other ingredients and then thoroughly mixed and slugged. The slugs are broken down by forcing then through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 50 mg of ibuprofen and 15 mg of morphine sulfate.

The foregoing tablets are useful for preventing pain following a broken femur by the oral administration of one tablet four times a day, for two days following setting the bone.

Using the procedure above, tablets are similarly prepared containing morphine sulfate in 7.5 mg and 3.75 mg amounts by substituting 7.5 gm and 3.75 gm of morphine sulfate for the 15 gm used above. These tablets are used to reduce the narcotic dose of the preceeding examples.

Example 4 Oral Suspension

One thousand ml of an aqueous suspension for oral use, containing in each teaspoonful (5 ml) dose, 100 mg of ibuprofen aluminum salt is prepared from the following types and amounts of ingredients:

Ibuprofen, aluminum salt micronized	20 gm
Citric acid	2 gm
Benzoic acid	1 gm
Sucrose	700 gm
Tragacanth	5 gm
Lemon oil	2 gm
Deionized water, q.s.	1000 ml

The citric acid, benzoic acid, sucrose, tragacanth and lemon oil are dispersed in sufficient water to make 850 ml of suspension. The ibuprofen aluminum salt (finely divided by means of an air micronizer) is stirred into the syrup until uniformly distributed. Sufficient water is added to make 1000 ml.

The composition so prepared is useful for preventing pain of cancer of the bowels at a dose of one tablespoonful (15 ml) four times a day with 1/4 gram of morphine sulfate given I.M. four times a day.

Example 5

A sterile aqueous solution for parenteral (i.v.) injection, containing in one liter, 350 mg of ibuprofen, sodium salt is prepared from the following types and amounts of ingredients:

Ibuprofen sodium salt	350 mg
Water for injection, q.s.	1000 ml

To the sterile solution is added sterilized ibuprofen, sodium salt and filled into sterile containers sealed.

The composition so prepared is useful for preventing pain of inoperable cancer at a dose of one liter every eight hours with 1/2 grain of morphine sulfate every eight hours.

Example 6 Hard Gelatin Capsules

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 50 mg of flurbiprofen and 15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

Flurbiprofen	50 gm
Morphine sulfate	15 gm
Lactose	100 gm
Corn starch	20 gm
Talc	20 gm
Magnesium stearate	2 gm

The flurbiprofen and morphine sulfate finely divided by means of an air micronizer, are added to the other finely powdered ingredients, mixed thoroughly and then encapsulated in the usual manner.

The foregoing capsules are useful for preventing pain following laparotomy by the oral administration of one capsule four times a day.

Using the procedure above, capsules are similarly prepared containing morphine sulfate in 7.5 and 3.75 mg amounts by substituting 7.5 and 3.75 gm of morphine sulfate for the 15 gm used above. These capsules are used to reduce the narcotic dose of the preceeding examples.

Example 7 Soft Gelatin Capsules

One-piece soft gelatin capsules for oral use, each containing 50 mg of flurbiprofen and 15 mg of morphine sulfate (finely divided by means of an air micronizer) are prepared by first suspending the compounds in 0.5 ml of corn oil to render the material capsulatable and then capsulating in the above manner.

The foregoing capsules are useful for preventing pain following caesarian section by the oral administratin of one capsule four times a day.

Example 8 Tablets

One thousand tablets, each containing 50 mg of flurbiprofen and

15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

Flurbiprofen micronized	50 gm
Morphine sulfate	15 gm
Lactose	75 gm
Corn starch	50 gm
Magnesium stearate	4 gm
Light liquid petrolatum	5 gm

The flurbiprofen and morphine sulfate (finely divided by means of an air micronizer) are added to the other ingredients and then thoroughly mixed and slugged. The slugs are broken down by forcing then through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 50 mg of flurbiprofen and 15 mg of morphine sulfate.

The foregoing tablets are useful for preventing pain following a broken femur by the oral administration of one tablet four times a day, for two days following setting the bone.

Using the procedure above, tablets are similarly prepared containing morphine sulfate in 7.5 mg and 3.75 mg amounts by substituting 7.5 gm and 3.75 gm of morphine sulfate for the 15 gm used above. These tablets are used to reduce the narcotic dose of the preceeding examples.

Example 9 Oral Suspension

One thousand ml of an aqueous suspension for oral use, containing in each teaspoonful (5 ml) dose, 100 mg of flurbiprofen aluminum salt is prepared from the following types and amounts of ingredients:

Flurbiprofen, aluminum salt micronized	20 gm
Citric acid	2 gm
Benzoic acid	1 gm
Sucrose	700 gm
Tragacanth	5 gm
Lemon oil	2 gm
Deionized water, q.s.	1000 ml

The citric acid, benzoic acid, sucrose, tragacanth and lemon oil are dispersed in sufficient water to make 850 ml of suspension. The flurbiprofen aluminum salt (finely divided by means of an air micronizer) is stirred into the syrup until uniformly distributed. Suf-

ficient water is added to make 1000 ml.

The composition so prepared is useful for preventing pain of cancer of the bowels at a dose of one tablespoonful (15 ml) four times a day with 1/4 gram of morphine sulfate given I.M. four times a day.

Example 10

A sterile aqueous solution for parenteral (i.v.) injection, containing in one liter, 350 mg of flurbiprofen, sodium salt is prepared from the following types and amounts of ingredients:

Flurbiprofen sodium salt	350 mg
Water for injection, q.s.	1000 ml

To the sterile solution is added sterilized flurbiprofen, sodium salt and filled into sterile containers sealed.

The composition so prepared is useful for preventing pain of inoperable cancer at a dose of one liter every eight hours with 1/2 grain of morphine sulfate every eight hours.

Example 11

Following the procedure of the proceeding Examples 1 through 10, inclusive, compositions are similarly prepared substituting equimolar amounts of the ester, e.g., methyl, ethyl, isopropyl, octyl or salts, e.g., sodium, potassium, ammonium, for the compound of the examples.

Example 12

Following the procedure of the preceeding Examples 1 through 10, inclusive, a dosage unit and regimen is similarly followed substituting an equi-analgesic amount each of: hydromorphone, oxymorphone, levorphanol, methandone, meperidine, alphapradine, fentanol, hydrocodone, oxycodone or codeine for the morphine of the examples.

C L A I M S

1. A process for treating pain by the systemic administration to a subject of a narcotic analgesic and ibuprofen or flurbiprofen, or a C_{1-8} alkyl ester or a pharmacologically acceptable salt thereof.

2. A composition comprising a narcotic analgesic and ibuprofen or flurbiprofen, or a C_{1-8} alkyl ester or a pharmacologically acceptable salt thereof.

3. A composition according to claim 2, which additionally comprises a physiologically-acceptable excipient.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

0068838
Application number

EP 82 30 3318

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	DE - A - 1 941 583 (ELI LILLY AND COMPANY) * page 11, claim 1 * & GB - A - 1 250 582	2-3	A 61 K 31/485 // (A 61 K 31/485 31/19) // (A 61 K 31/485 31/215)
A	CHEMICAL ABSTRACTS, vol. 90, no. 5, January 29, 1979 abstract no. 33960z, page 39 COLUMBUS, OHIO (US) & CLIN. EXP. PHARMACOL. PHYSIOL. 1978, 5(5), 503-9 D.N. SRIVASTAVA et al.: "Effect of some prostaglandin synthesis inhibitors on the antinociceptive action of morphine in albino rats" * abstract *	2-3	TECHNICAL FIELDS SEARCHED (Int. Cl. ³) A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 2,3

Claims searched incompletely:

Claims not searched: 1

Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (see article 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
The Hague	30-09-1982	BRINKMANN

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503.1. 03.82

PII-7

A COMPARISON OF METHODS TO MEASURE ONSET OF ANALGESIA. PJ Desjardins, DMD, PhD, P Black*, MS, M Milles*, DDS, G Mardirossian *, DMD, L Norris*, DMD, MPH and E McAuley*, UMDNJ, Newark, NJ, Tufts Univ, Boston, MA

This double-blind, randomized trial was designed to compare and validate two stopwatch techniques for measuring onset of analgesia. Patients received ibuprofen 400 mg (N=41) or placebo (N=19) for post-impaction pain. Patients actuated two stopwatches when they took the study medication, stopped the first when they felt "any" relief and stopped the second when they felt "meaningful" relief. A McGill Pain Questionnaire and a functional pain index were completed at baseline, onset of any relief, onset and offset of meaningful relief. 88% of IBU treated patients experienced some relief vs 63% of PLA treated patients ($P<.02$). In contrast, 81% vs 32% reported meaningful relief after IBU and PLA respectively ($P<.001$). Mean time to onset of any relief after IBU was 21 min vs 42 min for meaningful relief. The MPQ and function scores showed the greatest reductions from baseline ($P<.001$) when meaningful relief was reported. Assessments of onset of meaningful pain relief may provide more sensitive measures of drug effect than measures of first perceptible effect.

PII-8

ANALGESIC EFFICACY OF IBUPROFEN WITH HYDROCODONE VS. IBUPROFEN ALONE IN POSTOPERATIVE PAIN. A. Sunshine, M.D.[1,2], N.Z. Olson, M.P.S.[2], E. O'Neill, M.D.[3], I. Ramos, R.N.[3], S.A. Karpow, Pharm.D.[4], and R.T. Doyle, B.A.[4], NYU Medical Center; NY, NY; Analgesic Development Ltd[2], NY, NY; Municipal Hospital[3], PR; and Knoll Pharmaceuticals, Whippany, NJ[4].

The analgesic efficacy of ibuprofen 400mg with hydrocodone bitartrate 15mg (IB+H) was compared with ibuprofen 400mg (IB) and placebo (PL) in 120 patients with moderate or severe postoperative pain. Analgesia was measured based on onset of relief, hourly and summary variables, and duration of effect. A significantly greater proportion of patients treated with IB+H reported onset of relief compared to IB or PL; however, the distribution functions, and median times for onset were not significantly different. IB+H and IB were significantly more effective than PL for all pain measures. IB+H was significantly superior to IB for all hourly scores, SPID, and TOTPAR. No patient treated with IB+H required remedication during the 6 hr study period compared to 25% and 79% with the IB and PL treated patients, respectively. The probability of no longer having relief by hr 6 was .78 for PL, .18 for IB, and .00 for IB+H, and IB+H was significantly different from PL and IB. The addition of hydrocodone 15mg to ibuprofen 400mg significantly enhances the analgesic effect of ibuprofen.

PII-9

ANALGESIC EFFICACY OF AN IBUPROFEN-OXYCODONE COMBINATION. S.A. Cooper, DMD, Ph.D+, B. Haber, DDS*, J. Ilacqua, DDS*, N. Glauda, DDS* & C. Lamp, RN*, Temple Univ Sch Dentistry+, Phila, PA.

There are no narcotics combined with a new generation NSAID. This was a single dose, parallel group, double-blind, factorial design clinical trial. Treatments were ibuprofen 400 mg + oxycodone 5 mg (I+OX,n=47), ibuprofen 400 mg (I400,n=37) and placebo (PLA,n=24). Study patients had pain due to surgical removal of impacted teeth. Analgesic responses were recorded for up to 6 hours. Areas under the curve (AUC) for relief and pain intensity difference (PID) were analyzed using ANOVA and LSD tests. Both I400 and I+OX were significantly better than PLA at every hourly observation and for all other measures of efficacy. I+OX was statistically superior to I400 for relief hours 4-6, PID hours 5-6 and AUC PID. Compared to I400, I+OX had the longest time to rescue analgesic (282 vs 242 mins) and the highest % analgesic responders (68% vs 51%). The combination also had the highest incidence of side effects.

PII-10

A SINGLE DOSE STUDY EVALUATING THE ANALGESIC EFFICACY OF HYDROCODONE /ACETAMINOPHEN, OXYCODONE/ACETAMINOPHEN AND PLACEBO FOLLOWING ORAL SURGERY. P. Brown, R.N.*[1], D. R. Mehlisch[1], T. Kiersch*[3], G. Allan*[2], T. Sims*[1], Biomedical Research Group, Inc.[1], Austin, TX; Whitby Research, Inc., Richmond, VA.[2], Tucson, AZ[3].

This unbalanced (2:2:1 ratio), single dose, randomized, parallel, double-blind, placebo-controlled study was conducted at two sites, 323 male or female patients, 15-60 years old with moderate to severe dental pain were enrolled. The objective of this study was to compare 10 mg hydrocodone bitartrate with 500 mg acetaminophen (HBA) and 5 mg oxycodone hydrochloride with acetaminophen 325 mg (OHA). Primary efficacy variables were TOTPAR-6, PAID-6 and SPAID-6. There was a significant difference among treatment groups with respect to peak pain, TOTPAR-6, TOTPAR-4, pain relief evaluations and in the percent of patients taking backup pain medication. There was a significant difference in the percent of patients completing six hours of the study and patients reaching complete pain relief among treatment groups. This study demonstrated that both HBA and OHA are safe medications for use in patients undergoing oral surgery.

EVALUATION OF PAIN INTENSITY

Efficacy Parameter	Mean			Two-Way ANOVA			
	HBA	OHA	PLACEBO	P-Value Drug	OHA v Placebo	OHA v HBA	HBA v Placebo
Maximum PID	1.26	1.07	0.60	0.0001	Sig		Sig
SPID-6	3.86	2.62	1.57	0.0001	Sig	Sig	Sig
SPID-4	2.98	2.30	1.00	0.0001	Sig		Sig

J Oral Maxillofac Surg
57:673-678, 1999

Additive Analgesic Effects of Oxycodone and Ibuprofen in the Oral Surgery Model

*Raymond A. Dionne, DDS, PhD**

Purpose: A traditional approach to achieve greater analgesic efficacy is to combine an efficacious dose of a nonopioid with a dose of an opioid sufficient to produce additive analgesia without a substantial increase in the incidence of adverse effects. This study evaluated the additive analgesic effects of the combination of ibuprofen and oxycodone.

Patients and Methods: A dose of 400 mg ibuprofen was compared with 400 mg ibuprofen with oxycodone in doses of 2.5, 5, or 10 mg in the oral surgery model of acute pain. Analgesic efficacy was measured with category and visual analog scales at 15, 30, 45, and 60 minutes and hourly up to 6 hours.

Results: Ibuprofen plus 10 mg oxycodone produced significantly greater analgesia compared with the other three groups, as measured by the visual analog scale from 15 minutes after drug administration up to the 2-hour observation. All four treatments were similar from 3 to 6 hours, with the area under the pain intensity difference curve being similar across groups. Neither the 2.5-mg nor the 5-mg oxycodone dose provided any additive analgesia over ibuprofen at any points. Addition of oxycodone resulted in a dose-related increase in the number of patients reporting adverse effects, with significantly greater drowsiness and vomiting at the 10-mg dose.

Conclusions: These results indicate that additive analgesia can be achieved for the combination of a nonsteroidal anti-inflammatory drug and an orally effective opioid, with faster onset of relief for the combination of 400 mg ibuprofen and 10 mg oxycodone over the first 2 hours after administration, but at the expense of an increased incidence of adverse events.

Despite the well-documented efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) and the inflammatory origin of dental pain, some patients do not receive adequate relief from a normal therapeutic dose of an NSAID. Because of the relatively flat dose-response relationship for NSAIDS, increasing the dose beyond the maximum recommended will produce a marginal increase in analgesic activity but with an increased incidence of adverse effects. Switching to a combination such as acetaminophen plus codeine usually results in less analgesia and produces more side effects than when an NSAID is included. Analgesic adjuvants other than opioids (caffeine, barbiturates, or phenothiazines) have been removed from most drug combinations because of lack of additive analgesia activity at the doses used or concern for safety (phenacetin). These limitations of currently available analgesics and combinations result in a therapeutic dilemma of balancing less than optimal analgesia against increased side effect liability and concern for safety with chronic administration.

The traditional approach to overcoming these well-recognized limitations is to combine a therapeutic dose of a nonopioid, to achieve the maximal possible analgesia through one mechanism of action, with the minimal dose of an opioid that provides additive analgesia but without an unacceptable increase in the incidence of adverse effects. This forms the basis for classic analgesic combinations such as acetaminophen or aspirin plus codeine or oxycodone. An obvious combination based on this concept is to combine a therapeutic dose of an NSAID such as 400 mg ibuprofen with a dose of an opioid that produces additive analgesia, but with an acceptable incidence of adverse effects. However, the ability to demonstrate an additive effect for an opioid in combination with an NSAID has proved difficult. Codeine in doses of 20 to 60 mg has been evaluated in combination with varying doses of ibuprofen. Results using 200 mg ibuprofen plus 15 mg codeine were indistinguishable from ibuprofen 200 mg over the course of 5 hours postoperatively.[1] Similarly, the addition of 20 mg codeine to a sustained-release formulation of 300 mg ibuprofen did not result in any additive effects, but did produce a greater incidence of side effects.[2] Comparison of 400 mg ibuprofen plus 60 mg codeine to ibuprofen 400 mg

*Senior Investigator, Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD.

Address correspondence and reprint requests to Dr Dionne: National Institutes of Health, 10 Center Dr, Room 1N-103, Bethesda, MD 20892; e-mail: dionne@yoda.nidr.nih.gov

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also failed to show analgesia for the initial dose but tended to provide greater analgesia over the next 3 days, with only a modest increase in side effects.[3] The results of these and other studies[4-7] provide equivocal evidence for the additive effects of codeine in the range of 20 to 60 mg when administered in combination with ibuprofen 400 mg. As is usually seen for therapeutic doses of codeine in ambulatory patients, this additive analgesic effect is accompanied by an increased incidence of side effects such as drowsiness, dizziness, nausea, and vomiting.

Analgesic combinations containing oxycodone are generally perceived as more efficacious than codeine-containing combinations. This appears logical given the 10- to 12-fold greater potency attributed to oxycodone in comparison with codeine,[8,9] and administration of the recommended oxycodone dose in these combinations (5 mg every 6 hours) should result in analgesia equivalent to the usual 60 mg dose of codeine in analgesic combinations. The therapeutic advantage to oxycodone combinations is the ability to administer two tablets, a dose of 10 mg oxycodone, to produce greater analgesia.[10] The current study combined 400 mg ibuprofen with varying doses of oxycodone to determine whether an additive effect of an opioid could be demonstrated in combination with a normal therapeutic dose of an NSAID. The results suggest that while additive analgesia can be achieved at the highest dose of oxycodone evaluated, the side effect liability is substantial, and use of this combination should be reserved for clinical situations where the additional analgesia is required.

Patients and Methods

Subjects were oral surgery outpatients undergoing the surgical removal of two to four impacted third molars with midazolam sedation and local anesthesia using 2% lidocaine with 1:100,000 epinephrine. A mucoperiosteal flap was raised and retracted, bone was removed, and the teeth sectioned as needed to facilitate extraction. Sutures were used to close the surgical flap, a gauze was placed over each extraction site, and patients were moved to the recovery room for observation and postoperative data collection. Potential subjects were excluded if they had a history of an allergic or adverse reaction to any medication, a history of drug abuse or dependence, and if they had taken an analgesic, anti-inflammatory, or central nervous system depressant drug (with the exception of the midazolam used for the procedure) within 48 hours before oral surgery. Female patients of childbearing potential and not using an effective method of contraception also were excluded.

After surgery, subjects were questioned every 15 minutes regarding the loss of mandibular anesthesia and the onset of pain using category scales. At the report of "moderate" pain consistent with the offset of anesthesia, subjects completed a 100-mm visual analog scale for pain intensity and were then randomly allocated to one of the four treatments: ibuprofen 400 mg, ibuprofen 400 mg plus 2.5 mg oxycodone, ibuprofen 400 mg plus 5 mg oxycodone, or ibuprofen 400 mg plus 10 mg oxycodone.

Subjects completed questionnaires for pain intensity and pain relief at 15, 30, 45, 60 minutes, and hourly up to 6 hours after drug administration. Pain intensity was rated with a category scale as none (0), mild (1), moderate (2), or severe (3) and with a 100-mm visual analog scale (VAS) with a left endpoint of "none" and a right endpoint of "worse possible pain." These data were used to derive a pain intensity difference score at each time point by subtracting the starting pain value from each of the pain intensity ratings at each subsequent observation. Pain relief was rated with a five-point category scale as no pain relief (0), a little pain relief (1), some pain relief (2), a lot of relief (3), or complete relief (4) and with a VAS with a left endpoint of "no relief" and a right endpoint of "complete relief."

Data were analyzed with the BMDP Statistical Software Package (SPSS, Inc., Chicago, IL). Statistical differences between treatments for VAS data were determined by repeated measures analysis of variance over the first 2 hours after administration as a measure of early analgesic activity and for the entire 6-hour observation period. The source and magnitude of differences between treatments at each time were determined by one-way analysis of variance with post hoc comparisons by Duncan's multiple range test. Categorical data were compared with the Kruskal-Wallis test. For all statistical tests, differences in P values $< .05$ in a two-tailed test were considered significant. A sample size of 30 subjects per group was calculated based on a previous study using the oral surgery model.[11]

Results

The study sample consisted of 118 usable subjects equally distributed among the four drug groups (Table 1). The mean age was characteristic of the young adult population normally undergoing the removal of impacted third molars and did not differ substantially between groups in gender distribution, height, weight, doses of adjunctive drugs administered, or difficulty of the surgical procedures. The mean starting pain as measured by category scale (2.2 to 2.4) and VAS (61.8 to 67.3) were very similar between groups. The similarity of the prognostic factors for postoperative

	N	Age	Gender	Height (cm)	Weight (kg)	Midazolam (mg)	Lidocaine (mg)	Surgical Difficulty*
Ibuprofen 400	29	21.6 ± 3.7	18 F 11 M	170.7 ± 10.2	64.3 ± 9.7	4.8 ± 0.6	186.6 ± 44.6	11.3 ± 3.9
Ibuprofen 400 mg Oxycodone 2.5 mg	29	21.5 ± 5.6	11 F 18 M	175.5 ± 10.9	69.9 ± 11.6	4.8 ± 0.8	189.0 ± 30.1	12.6 ± 3.0
Ibuprofen 400 mg Oxycodone 5 mg	29	20.8 ± 5.4	18 F 11 M	169.4 ± 10.4	65.4 ± 14.5	4.6 ± 0.8	185.6 ± 34.0	13.1 ± 2.5
Ibuprofen 400 mg Oxycodone 10 mg	31	22.1 ± 6.2	21 F 10 M	167.4 ± 7.9	63.7 ± 10.3	4.9 ± 1.1	197.8 ± 49.6	12.7 ± 3.2

*Surgical difficulty classified as simple extraction (1), soft tissue impaction (2), partial bony impaction (3), or full bony impaction (4); value is sum for all teeth extracted.

pain (difficulty of the surgical procedure and starting pain) and the demographic characteristics of the groups indicated that these factors did not likely confound the outcome of the study.

Analgesic effect, as measured by the VAS pain intensity difference, showed significantly greater effect for the combination of ibuprofen plus 10 mg oxycodone at 15, 30, 45, and 60 minutes and at 2 hour after drug administration in comparison to ibuprofen 400 mg alone (Fig 1, upper panel). Analgesic effect reached a peak between 2 and 4 hours, followed by a gradual decrease over the last 2 hours of the observation period. None of the treatments could be separated from each other at any of the observation periods from 3 to 6 hours. The sum of the pain intensity difference scores over the first 2 hours during analgesic onset was significantly greater for the oxycodone 10 mg plus ibuprofen 400 mg than for the ibuprofen 400 mg alone (Fig 1, lower panel) but did not differ between treatments for the sum of the 6 hours. Similar, but nonsignificant, trends were seen between treatments for the pain intensity difference scores as measured by category scale (data not shown).

The pain relief VAS showed similar trends for greater relief from the combination of ibuprofen plus 10 mg oxycodone at the early time points, but no difference between treatments over the last 2 to 6 hours (Table 2), or for the sum of the pain relief scores for the entire observation period. Pain relief measured by category scale showed greater, but nonsignificant, mean scores for the combination of ibuprofen plus 10 mg oxycodone at each observation from 30 minutes to 2 hours, but did not differ at later points (Table 2).

The incidence of adverse effects was low in the ibuprofen 400 mg group and were not significantly increased by the addition of 2.5 mg or 5 mg oxycodone (Table 3). The addition of 10 mg oxycodone resulted in a significant increase in the incidence of drowsiness ($P < .001$) and vomiting ($P < .05$), while decreasing the number of subjects who did not report any side effects to 5 of the 31 who received this dose.

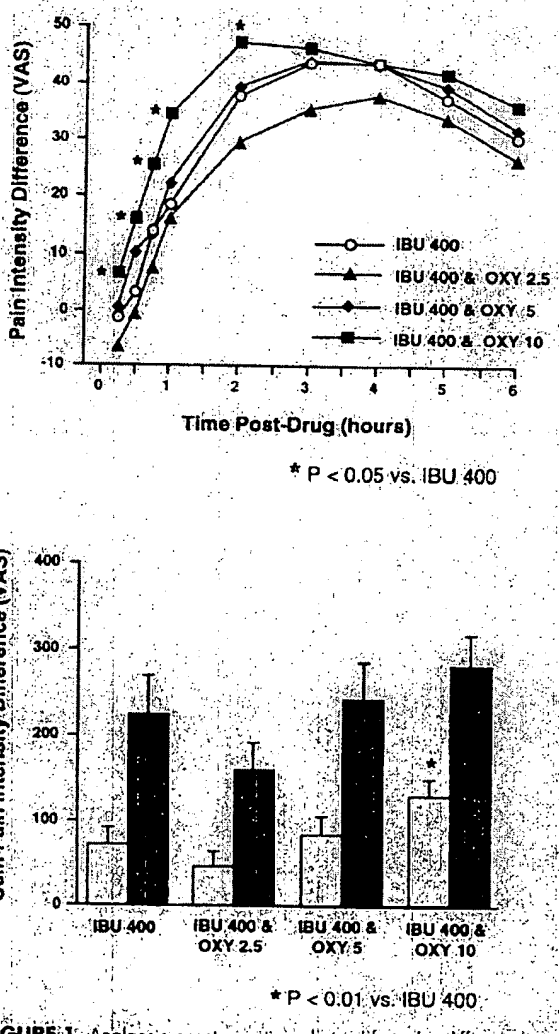

FIGURE 1. Analgesic onset over time derived from the difference in pain intensity from baseline as measured by visual analog scale (upper panel). Sum of the pain intensity difference scores for the first 2 hours during analgesic onset (left bar) and for the entire 6-hour observation period (right bar) for each of the four treatment groups (lower panel).

	Time Post-Surgery (min)								
	15	30	45	60	120	180	240	300	360
Pain relief (VAS)									
Ibuprofen 400	11.9 ± 14.7	23.1 ± 25.8	40.5 ± 32.8	43.9 ± 32.0	68.6 ± 28.6	72.6 ± 31.5	75.5 ± 33.3	70.8 ± 35.1	61.1 ± 42.1
Ibuprofen 400 Oxycodone 2.5	9.7 ± 14.7	18.6 ± 20.8	28.4 ± 29.0	35.4 ± 29.7	60.7 ± 29.0	67.0 ± 31.5	70.3 ± 30.3	65.7 ± 36.7	59.2 ± 37.5
Ibuprofen 400 Oxycodone 5	13.3 ± 21.3	27.2 ± 28.0	35.0 ± 30.4	42.7 ± 34.5	64.9 ± 33.0	69.8 ± 35.3	71.2 ± 34.1	66.5 ± 35.1	62.1 ± 35.3
Ibuprofen 400 Oxycodone 10	16.4 ± 22.5	34.4 ± 32.7*	44.8 ± 33.2	53.8 ± 32.8*	71.6 ± 28.9	71.7 ± 31.1	68.0 ± 35.1	65.0 ± 36.6	60.3 ± 40.6
Pain Relief (Category)									
Ibuprofen 400	0.6 ± 0.7	1.0 ± 1.0	1.7 ± 1.2	1.7 ± 1.2	2.6 ± 1.2	2.7 ± 1.3	2.9 ± 1.3	2.6 ± 1.4	2.2 ± 1.5
Ibuprofen 400 Oxycodone 2.5	0.5 ± 0.6	0.8 ± 0.8	1.3 ± 1.1	1.7 ± 1.0	2.4 ± 1.0	2.6 ± 1.2	2.7 ± 1.1	2.4 ± 1.4	2.3 ± 1.4
Ibuprofen 400 Oxycodone 5	0.7 ± 0.9	1.2 ± 1.1	1.6 ± 1.2	1.9 ± 1.2	2.5 ± 1.2	2.6 ± 1.3	2.6 ± 1.3	2.5 ± 1.3	2.3 ± 1.3
Ibuprofen 400 Oxycodone 10	0.7 ± 0.9	1.4 ± 1.2	1.9 ± 1.2	2.2 ± 1.2	2.8 ± 1.1	2.7 ± 1.2	2.6 ± 1.3	2.5 ± 1.4	2.3 ± 1.5

*$P < .05$ vs IBU 400.

Discussion

The current study attempted to determine a dose of an orally effective opioid that produced an optimal additive effect by evaluating a range of opioid doses that would be predicted to span from a subtherapeutic dose (2.5 mg), including the dose normally used in combination with a nonopioid (5 mg), and a dose producing greater analgesia (10 mg). Consistent with this hypothesis, the combination of ibuprofen 400 mg plus oxycodone 2.5 mg did not result in any additive analgesic effects. However, the combination of ibuprofen with 5 mg oxycodone also did not result in any detectable additive effects on any of the four analgesic scales used at any point. The 10-mg oxycodone dose produced additive analgesic effects, but only at the early points when the onset of racemic ibuprofen was still increasing. This advantage was not detectable at any times from 3 to 6 hours, with all four groups resulting in similar overall area under the analgesic time response curve. These data suggest that the only advantage to adding an opioid to an NSAID in the oral surgery model is at times when the onset of analgesic activity of the NSAID component of the combination is suboptimal; presumably because the delay inherent in the conversion of the relatively inactive R(−)-isomer of ibuprofen to the active S(+)-isomer.[12]

This additive effect of the 10-mg dose is at the expense of a high incidence of central nervous system-mediated adverse effects. Only 16% of subjects in this group did not report side effects, in comparison to 62% of symptom-free subjects in the ibuprofen 400-mg group. Although it is likely that some of the side effects experienced over the first few hours postsurgically were related to residual effects of the midazolam sedation and central effects of local anesthetic absorption, these data suggest an approximate twofold increase in side effects due to the opioid. Yet, the overall analgesic effect over the 6-hour observation period was negligible and confined to the initial 2 hours postdrug administration. This relationship between transient, marginal additive analgesia at the expense of a substantial increase in side effect liability suggests a questionable therapeutic benefit.

An alternative to the delayed onset of analgesia in the oral surgery model is the well-documented effect of preventive analgesia. Administration of an NSAID such as ibuprofen[13] or flurbiprofen[14] before the offset of local anesthesia significantly attentuates the onset

	Drowsiness	Nausea	Vomited	Dizzy	Other	None
Ibuprofen 400	3	2	0	0	5	18/29
Ibuprofen 400 Oxycodone 2.5	6	2	2	1	5	17/29
Ibuprofen 400 Oxycodone 5	8	5	0	1	2	14/29
Ibuprofen 400 Oxycodone 10	20†	6	5*	5	6	5/31†

*$P < .05$.
†$P < .001$.

of pain in the oral surgery model, but without any appreciable increase in side effects in comparison with administering the same drug after pain onset. Additional benefit can be achieved by using a long-acting local anesthetic, such as etidocaine or bupivacaine, in combination with the NSAID pretreatment.[15] Although not commercially available in the United States, administration of the S-isomer of ibuprofen results in a faster onset and greater peak analgesia than administration of the same-milligrams dose of racemic ibuprofen.[12] No detectable increase in side effect incidence is associated with this therapeutic benefit, and the duration of drug action is comparable, indicating a favorable benefit-to-risk relationship.

Comparisons of analgesic activity in the oral surgery model is based on statistical analysis of grouped data from samples usually ranging from 20 to 50 per treatment. Although appropriate for clinical trials, this approach fails to account for the large variability that exists between patients in their response to the surgical procedure, the analgesic effects of the drug, and sensitivity to side effects. Virtually all studies using oral medications use fixed doses so that the actual dose (in mg/kg) varies according to body weight. Pharmacokinetic and pharmacogenetic differences also contribute to variability in analgesic responsiveness,[16] especially in the conversion of codeine to morphine-3-glucuronide, the presumed active metabolite of codeine.[17] These considerations make it unlikely that the analgesic effects for specific drugs and doses, especially when given in combination, can be generalized across the population of all patients. It is possible, based on the results of well-controlled trials, that an optimal dose of an NSAID might still be inadequate in a specific patient, whereas addition of an opioid resulting in a significant elevation in side effects for a group of subjects would be well tolerated by an individual patient.

The availability of oxycodone as a single-entity generic formulation permits optimization of the additive effects of an NSAID-opioid combination for each patient after an outpatient surgical procedure. The optimal dose of an NSAID can be administered to a patient before pain onset to block the effects of prostaglandin E_2 released in the postoperative period[18] due to the expression of cyclooxygenase-2. This dose should be continued on a "by-the-clock" basis, based on the recommended dosing interval for the drug, to avoid pain associated with the offset of analgesic activity and the delayed onset associated with the absorption, distribution, and pharmacolgic effects of subsequent doses. For pain that is unrelieved by this strategy, the minimal effective dose of oxycodone that results in an additive analgesic effect could be administered on an "as needed" basis for a minimal number of doses and adjusted between one and two 5-mg tablets to balance the additive analgesic effects against the likelihood of side effects. For some patients, a few doses of 5 mg oxycodone in combination with the NSAID should provide adequate analgesia and minimal side effects, while others may require 10 mg doses. At the very least, subjects who experience drowsiness may accept this as a reasonable alternative to inadequate pain relief. By administering the opioid selectively to patients who are experiencing suboptimal analgesia from an NSAID, only those patients receiving the therapeutic benefit are exposed to the potential risk of increased adverse effects. Conversely, administering a fixed-dose combination to all subjects would likely result in a spectrum of effects ranging from unnecessary adverse effects without therapeutic benefit, some patients having an optimal balance, and some patients having little additive analgesia but substantial side effects.

The availability of a fixed-dose combination of ibuprofen and an orally effective analgesic, hydrocodone, suggests the ability to achieve the additive effects of the NSAID-opioid combination without the need to individualize the opioid dose or deal with the regulatory issues associated with prescribing controlled substances. This formulation combines 200 mg ibuprofen with 7.5 mg hydrocodone, a dose that is approximately equivalent to a 45-mg dose of codeine.[19] As reviewed elsewhere,[20] administration of a single dose of this formulation results in a suboptimal dose of ibuprofen, equivalent to a single tablet of an over-the-counter formulation, with a near maximal dose of the opioid. Increasing the dose to two tablets will provide the normal therapeutic ibuprofen dose but with a dose of hydrocodone likely to produce a high incidence of adverse effects. Extrapolating from the results of the current study and the few published studies on the analgesic effectiveness of hydrocodone in the oral surgery model suggests that one tablet of the ibuprofen-hydrocodone combination should be combined with a 200- to 400-mg dose of ibuprofen to result in the maximal beneficial effects of the NSAID with an additive opioid effect. However, no published studies have evaluated this combination in the oral surgery model.

The results of this study show an additive effect for the most widely used NSAID when administered in combination with an orally effective opioid, in therapeutic doses of each agent, to patients without contraindications to either drug. Given the need to provide greater analgesia to some patients after surgical procedures, the combination of an NSAID and an opioid appears to provide a therapeutic alternative if preventive strategies have not proved effective or were not appropriate to the therapeutic environment. Optimization of the benefit-to-risk ratio associated with the combination can be best achieved by only administer-

ing the opioid to patients who need the additional analgesic benefit and titrating the dose on the basis of side effects.

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Basics of Anesthesia

Fourth Edition

Robert K. Stoelting, M.D.
Professor and Chair
Department of Anesthesia
Indiana University School of Medicine
Indianapolis, Indiana

Ronald D. Miller, M.D.
Professor and Chair
Department of Anesthesia and Perioperative Care
University of California, San Francisco, School of Medicine
San Francisco, California

CHURCHILL LIVINGSTONE
A Harcourt Health Sciences Company
New York Edinburgh London Philadelphia

CHURCHILL LIVINGSTONE
A Harcourt Health Sciences Company

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data

Stoelting, Robert K.

Basics of anesthesia / Robert K. Stoelting, Ronald D. Miller.—4th ed.

p. cm.

Includes bibliographical references and index.

ISBN 0-443-06573-X

1. Anesthesia. I. Miller, Ronald D., II. Title.

[1. Anesthesia. WO 200 S872b 2000] RD81 .S86 2000

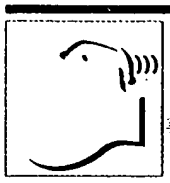
DNLM: 617.9'6—dc21 99-053883

Editor-in-Chief: Lisette Bralow
Acquisitions Editor: Allan Ross
Developmental Editor: Mia Carino
Project Manager: Mary Anne Folcher
Senior Production Manager: Linda R. Garber
Illustration Specialist: Peg Shaw
Book Designer: Steven Stave

BASICS OF ANESTHESIA ISBN 0-443-06573

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1



33

Acute Postoperative Pain Management

Acute postoperative pain is a complex physiologic reaction to tissue injury, visceral distension, or disease. Postoperative pain produces adverse physiologic effects with manifestations on multiple organ systems.[1] For example, pain following upper abdominal or thoracic surgery often leads to hypoventilation from splinting. This change promotes atelectasis, which impairs ventilation-to-perfusion relationships and increases the likelihood of arterial hypoxemia and pneumonia. Pain that limits postoperative ambulation combined with a stress-induced hypercoagulable state may contribute to an increased incidence of deep vein thrombosis.[2, 3] Catecholamines released in response to pain may result in tachycardia and hypertension, which may induce myocardial ischemia in susceptible patients.

With the development of an expanding awareness of the epidemiology and pathophysiology of pain, more attention is being paid to the management of postoperative pain in an effort to improve patient comfort, decrease perioperative morbidity, and decrease cost by shortening the time spent in postanesthesia care units, intensive care units, and hospitals.[3] The natural progression of this expanding awareness of the adverse physiologic effects of postoperative pain is the formation of acute pain management services, most often directed by an anesthesiologist.[4, 5] In this regard, the continuity of acute postoperative pain management is enhanced because the anesthesiologist is routinely involved in the preoperative assessment, intraoperative management, and postoperative followup of surgical patients.

The complexity of new analgesic techniques (patient controlled analgesia [PCA], neuraxial analgesia, peripheral nerve blocks) for the management of acute postoperative pain requires the adoption of written policies and procedures (medication protocols, algorithms, preprinted postoperative orders) to maximize efficacy while minimizing adverse effects (Tables 33–1 and 33–2).[1] Ultimately, the goals of the acute pain management service are (1) evaluation and treatment of postoperative pain and (2) identification and management of undesirable side effects related to postoperative analgesic techniques. This is a 24-hour-a-day commitment to postoperative patients by the anesthesiologist responsible for the acute pain manage-

Adverse Physiologic Effects of Postoperative Pain

- Pulmonary system (decreased lung volumes)
  - Atelectasis
  - Ventilation-to-perfusion mismatching
  - Arterial hypoxemia
  - Hypercarbia
  - Pneumonia
- Cardiovascular system (sympathetic nervous system stimulation)
  - Systemic hypertension
  - Tachycardia
  - Myocardial ischemia
  - Cardiac dysrhythmias
- Endocrine system
  - Hyperglycemia
  - Sodium and water retention
  - Protein catabolism
- Immune system (decreased immune function)
- Coagulation system
  - Increased platelet adhesiveness
  - Decreased fibrinolysis
  - Hypercoagulation
  - Deep vein thrombosis
- Gastrointestinal system
  - Ileus
- Genitourinary system
  - Urinary retention

Table 33–1. Important Elements of Intravenous Patient Controlled Analgesia (PCA) Preprinted Orders

1. Drugs, concentrations
2. Pump settings
   - Incremental dose
   - Lockout interval
   - Other limits
3. Mode of use
   - PCA only
   - Continuous infusion
4. Initial drug loading instructions
5. Instructions for treating breakthrough pain
6. A statement to prevent the ordering of central nervous system depressants by others
7. Monitoring instructions
8. Availability of drugs to treat side effects
9. Instructions for treatment of side effects
   - Depression of ventilation
   - Nausea and/or vomiting
   - Pruritus
   - Urinary retention
10. Instructions about concurrent use of other central nervous system depressants
11. Instructions for whom to contact if problems occur
12. Date, time, signature

(Modified from Ready LB, Ashburn M, Caplan RA, et al. Practice guidelines for acute pain management in the perioperative setting. Anesthesiology 1995;82:1071–1081, with permission.)

Table 33–2. Important Elements of Epidural Analgesia Preprinted Orders

1. Drug(s), concentration(s)
2. Instructions for administration
   - If boluses—drug dose and interval between injections
   - If infusion—loading dose and infusion rate
3. Instructions for treating breakthrough pain
4. Maintain intravenous access for immediate infusion of necessa drugs (naloxone)
5. A statement to prevent ordering of central nervous system d pressants by others
6. Monitoring instructions
   - For effects of opioids
   - For effects of local anesthetics—sensory and motor bloc hypotension, bradycardia
7. Observations and vital signs that should be communicated to t anesthesiologist
8. Instructions for treatment of side effects
   - Depression of ventilation
   - Nausea and vomiting
   - Pruritus
   - Urinary retention
9. Instructions about concurrent use of other central nervous sy tem depressants
10. Instructions for whom to contact if problems occur
11. Date, time, signature

(Modified from Ready LB, Ashburn M, Caplan RA, et al. Practice guid lines for acute pain management in the perioperative setting. Anesthesiolog 1995;82:1071–1081, with permission.)

ment service. In addition, there must be cooperation between anesthesiology, nursing, pharmacy, and surgery personnel.

NEUROPHYSIOLOGY OF PAIN

Understanding the mechanisms of pain and its pharmacologic modification is essential to optimal treatment of acute postoperative pain.

Nociception

Nociception describes the recognition and transmission of painful stimuli. Stimuli generated from thermal, mechanical, or chemical tissue damage may activate nociceptors, which are free afferent nerve endings of myelinated A-delta and unmyelinated C fibers (Fig. 33–1).[6] These peripheral afferent nerve endings send axonal projections into the dorsal horn of the spinal cord where they synapse with second order afferent neurons. Axonal projections of second order neurons cross to the contralateral hemisphere of the spinal cord and ascend afferent sensory pathways (spinothalamic tract) to the level of the thalamus (Fig. 33–1).[6] Along the way, these neurons divide and send axona branches to the reticular formation and the periaque ductal gray matter. In the thalamus, second order neu rons synapse with third order neurons, which sen axonal projections into the sensory cortex.

Modulation of Nociception

Modulation of nociception can occur at several lev els of the afferent sensory pathway prior to perceptio of pain at the sensory cortex. For example, modulatio of the painful impulse may occur at the origin of th stimulus (nociceptor) or at any point in the ascendin sensory afferent pathways where synaptic transmissio occurs (Fig. 33–1).[6] Furthermore, modulation of noci ception may occur through descending efferent inhibi tory pathways that originate at the level of the brai stem (Fig. 33–2).[6]

PERIPHERAL. Peripheral modulation of nociceptio occurs by either the liberation or elimination of endog enous mediators of inflammation in the vicinity of th nociceptor. These mediators sensitize (hyperalgesic ef fect) and excite nociceptors, especially in tissues tha have been subjected to trauma and inflammation. Aspi rin and nonsteroidal anti-inflammatory drugs (NSAIDs)

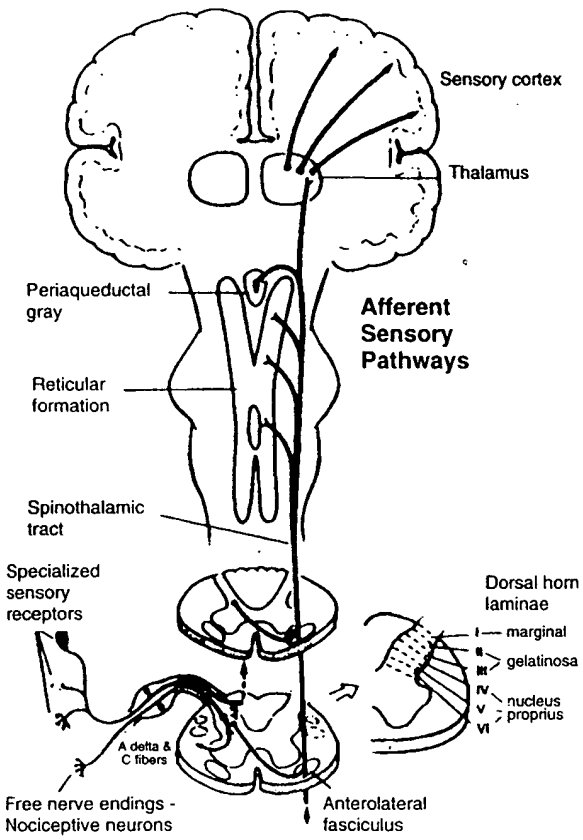


Figure 33–1. Afferent sensory pathways for recognition and transmission of painful stimuli. (From Lubenow TR, Ivankovich RD, McCarthy RJ. Management of acute postoperative pain. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical Anesthesia. Philadelphia. Lippincott-Raven 1997:1305–1338, with permission.)

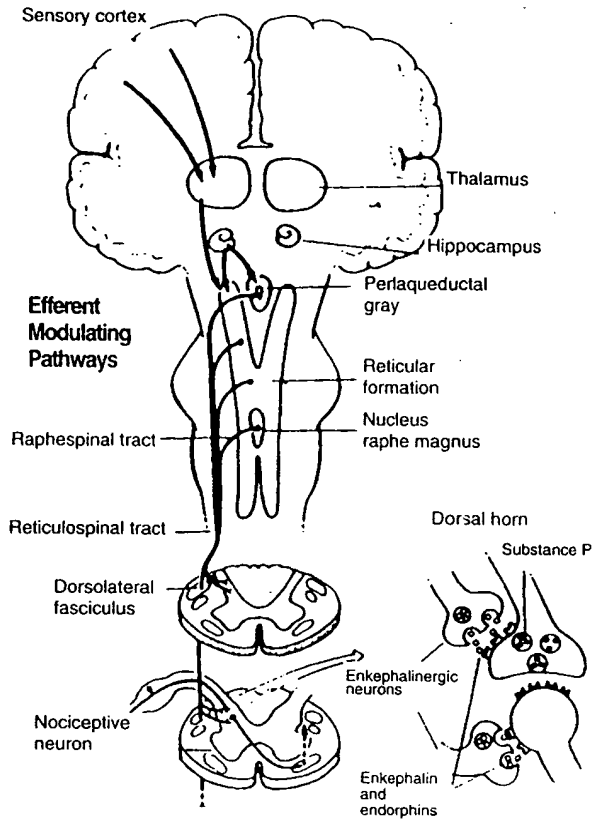


Figure 33–2. Descending efferent inhibitory (modulating) pathways involved in nociceptive regulation. (From Lubenow TR, Ivankovich RD, McCarthy RJ. Management of acute postoperative pain. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical Anesthesia. Philadelphia. Lippincott-Raven 1997:1305–1338, with permission.)

such as ketorolac decrease the synthesis of prostaglandins by inhibiting the action of the enzyme cyclooxygenase, which is necessary for the conversion of arachidonic acid to prostaglandins. By decreasing prostaglandin synthesis, these NSAIDs modulate (block) nociception at peripheral sites.

Endogenous Mediators of Inflammation
Prostaglandins ($PGE_1 > PGE_2$)
Histamine
Bradykinin
Serotonin
Acetylcholine
Lactic acid
Hydrogen ions
Potassium ions

SPINAL CORD. Modulation of nociception in the spinal cord results from the effects of excitatory or inhibitory neurotransmitters in the dorsal horn or by spinal reflexes which transmit efferent impulses back to peripheral nociceptors (Fig. 33–2).[6]

SUPRASPINAL. Modulation of nociception may occur through descending efferent inhibitory pathways that originate at the level of the brain stem and synapse in the substantia gelatinosa region of the dorsal horn (Fig. 33–2).[6] An opioid descending inhibitory pathway releases endorphins and enkephalins, which act presynaptically to hyperpolarize nerve fibers; this serves to negate the current (action potential) to the next synapse and subsequent release of neurotransmitters. Morphine and other exogenous opioids act as agonists at stereoselective membrane-bound receptors that are distributed throughout the central nervous system (see Table 6–2). In addition to the opioid descending inhibitory pathway, there is an alpha-adrenergic descending inhibitory pathway that terminates in the substantia gelatinosa region of the dorsal horn. Norepinephrine is released from these nerve terminals

and produces hyperpolarization of nerve fibers, which serves to negate the current to the next synapse and the subsequent release of neurotransmitters. Analgesic effects of clonidine most likely reflect its actions through this alpha-adrenergic inhibitory pathway.

Examples of Pain-Modulating Neurotransmitters

- Excitatory
  - Glutamate
  - Aspartate
  - Vasoactive intestinal polypeptide
  - Cholecystokinin
  - Gastrin-releasing peptide
  - Angiotensin
  - Substance P
- Inhibitory
  - Enkephalins
  - Endorphins
  - Substance P
  - Somatostatin

ANALGESIC DELIVERY SYSTEMS

Traditional delivery systems for management of acute postoperative pain as represented by oral and parenteral on-demand administration of analgesics are being replaced by more efficacious techniques such as neuraxial analgesia or PCA. New drug delivery techniques are based on an improved understanding of the neurophysiology of pain and the potential deleterious effects of postoperative pain. The formation of an acute pain management service directed by an anesthesiologist with expertise in regional anesthesia and the pharmacology of analgesics has facilitated the widespread application of these new analgesic delivery systems.

Oral Administration

Oral administration of analgesics is not considered optimal for management of moderate to severe acute postoperative pain, principally because of the lack of titratability and prolonged time to peak effect. Traditionally, postoperative patients are switched to oral analgesics (aspirin, acetaminophen, NSAIDs) when pain has diminished to the extent that the need for rapid adjustments in the level of analgesia is unlikely. Nevertheless, with the increased complexity of outpatient surgical procedures, there is a growing need for oral analgesics that are efficacious in the treatment of moderate to severe acute postoperative pain. Transmucosal delivery of analgesics such as fentanyl may serve as an alternative to oral administration of NSAIDs, especially when a prompt drug effect is desirable.

Routes of Delivery for Analgesic Drugs

- Oral
- Transmucosal
- Transdermal
- Intramuscular
- Intravenous
  - Intermittent
  - Continuous
  - Patient controlled
- Neuraxial
  - Epidural (continuous and patient controlled)
  - Intrathecal
- Peripheral nerve block
- Intrapleural regional analgesia
- Transcutaneous electrical nerve stimulation

Intramuscular Administration

Intramuscular administration of analgesics is the traditional method for treating moderate to severe postoperative pain, providing a more rapid onset and time to peak effect than oral analgesics. Nevertheless, plasma concentrations of opioids achieved after intramuscular administration may vary as much as three- to fivefold.[7] Plasma concentrations of opioids following intramuscular administration on a fixed time interval (typically every 3 to 4 hours) result in a cyclic period of sedation, analgesia, and, finally, inadequate analgesia.[8] It is estimated that plasma concentrations will exceed or equal analgesic concentrations only 35% of the time during such a fixed dosing interval. As a result, an estimated 75% of patients receiving intermittent intramuscular opioids postoperatively remain in moderate to severe pain.[4] Delivery of opioids by PCA circumvents many of the problems of intramuscular opioid administration and is predicted to provide more effective analgesia with fewer side effects by maintaining plasma concentrations in a more narrow but analgesic range (see the section *Patient Controlled Analgesia).* An alternative to intramuscular administration of opioids is the injection of ketorolac, an NSAID with efficacy equal to that of moderate doses of opioids but lacking depressant effects on ventilation.

Table 33–3. Guidelines for Delivery Systems Used in Patient Controlled Analgesia

	Bolus Dose (mg)	Lockout Interval (min)	Continuous Infusion (mg/h)	Four Hour Limit (mg)
Morphine	0.5–3	5–20	1–10	20–30
Meperidine	5–15	5–15	5–40	200–300
Fentanyl	0.015–0.05	3–10	0.02–0.1	0.2–0.4
Sufentanil	0.003–0.015	3–10	0.004–0.03	

Intravenous Administration

Intermittent intravenous administration of small doses of opioids (morphine 0.5 to 3 mg, fentanyl 15 to 50 μg, sufentanil 3 to 15 μg) is commonly used to treat acute and severe pain in the postanesthesia care unit or intensive care unit where continuous nursing surveillance and monitoring (pulse oximetry) are available. With a small intravenous dose of an opioid, the time delay for analgesia and variability in plasma concentrations characteristic of intramuscular injections are minimized. Rapid redistribution of the opioid will shorten the duration of analgesia after a single intravenous administration compared with an intramuscular injection.

Patient Controlled Analgesia

PCA is dependent on the use of drug delivery systems that allow the patient to titrate analgesic needs by activating a switch that results in the intravenous delivery of a solution containing a small dose of an opioid. Limits are placed on the number of activations per unit of time that will respond to the patient's utilization of the delivery system, and there is also a minimum time interval that must elapse between activations (lockout interval) (Table 33–3).[5] It is also possible for these delivery devices to record a profile of the drug administration, including the number and time of bolus delivery, number of activations that did not result in drug delivery, and total amounts of drug that were administered per time unit. Further refinement of these delivery systems permits the physician to administer a continuous background intravenous infusion of opioid superimposed on patient controlled boluses. Most patients tend to determine a level of pain which they view as acceptable and taper their dosage requirements as they convalesce. Patient acceptance of PCA is high since patients feel that they have significant control of their therapy. Compared with traditional methods of intermittent intramuscular injections of opioids to manage acute postoperative pain, PCA provides better analgesia with less total drug usage, less sedation, fewer nocturnal sleep disturbances, and a more rapid return to physical activity.[9]

Postoperative Patient Controlled Analgesia Order Sheet

Morphine 30 mg per 30 ml prefilled syringe
Loading dose 2 mg IV (range 1 to 4 mg)
Maintenance dose 1 mg IV
Lockout interval 8 minutes (range 6 to 10 minutes)
Limit dose to 20 mg over 4 hours (may be increased to 30 mg if inadequate analgesia)
Monitor vital signs as ordered
Assess pain level and effectiveness of PCA as ordered
Record drug administered every 8 hours

Neuraxial Analgesia

Placement of an opioid in the intrathecal or epidural space (neuraxial placement) to manage acute postoperative pain is based on the knowledge that opioid receptors are present in the substantia gelatinosa of the spinal cord.[10] Presumably, opioids placed in the epidural space diffuse across the dura to gain access to opioid receptors on the spinal cord. Analgesia produced by neuraxial opioids, in contrast to intravenous administration of opioids or regional anesthesia with local anesthetics, is not associated with sympathetic nervous system denervation, skeletal muscle weakness, or loss of proprioception. As a result, it is possible to render postoperative patients pain free without interfering with their ability to ambulate. There is evidence that neuraxial analgesia improves postoperative pulmonary function, decreases cardiovascular and infectious complications, and decreases total hospital costs.[2, 3]

Side Effects

Side effects of neuraxial opioids are due to the presence of drug in the cerebrospinal fluid and/or systemic circulation (see Table 6–3). Early depression of ventilation (within 2 hours of neuraxial administration) reflects systemic absorption of opioid from its epidural placement site, whereas delayed depression of ventilation (6 to 12 hours after neuraxial administration) is due to cephalad spread of the opioid in cerebrospinal fluid and interaction with opioid receptors located in the medullary centers in the area of the fourth cerebral ventricle.

Factors that increase the risk of delayed depression of ventilation, especially concomitant use of any intravenous opioids or sedatives, must be considered in determining the total dose of neuraxial opioid (see Table 6–4).[11] Detection of depression of ventilation induced by neuraxial opioids may be difficult. Pulse oximetry reliably detects opioid-induced arterial hypoxemia, and supplemental oxygen is an effective treatment.[12] A depressed level of consciousness in a patient being treated with neuraxial opioids should arouse suspicion of opioid-induced depression of ventilation. Opioids with a high lipid solubility, such as fentanyl or sufentanil, attach to lipid components in the spinal cord; therefore, less drug is available to diffuse cephalad, making delayed depression of ventilation less likely than after injection of poorly lipid soluble morphine.

Intrathecal Administration

Intrathecal administration of an opioid provides long-lasting postoperative analgesia after a single injection. The intrathecal route offers the advantage of precise and reliable placement of low concentrations of drug near its site of action.[13] The onset of analgesic effect following the intrathecal administration of an opioid is directly proportional to the lipid solubility of the drug, whereas the duration of effect is longer with more hydrophilic compounds. Morphine, for example, has been shown to produce peak analgesic effects in 20 to 60 minutes and provide postoperative analgesia for 12 to 36 hours. The onset of analgesic effect may be enhanced by adding a small dose of fentanyl to the morphine-containing opioid solution. For example, intrathecal placement of morphine (0.6 to 0.8 mg) plus fentanyl (25 μg) at the conclusion of a thoracotomy is likely to permit an early onset of analgesia. As a result, the patient is able to breathe deeply without pain, and the trachea can often be extubated at the conclusion of surgery. This analgesia may be supplemented by the intraoperative performance of intercostal nerve blocks by the surgeon. For lower abdominal procedures performed with spinal anesthesia (cesarean section, transurethral resection of the prostate), morphine (0.2 to 0.4 mg) may be added to the local anesthetic solution at the time the anesthetic is performed to ensure analgesia at the conclusion of surgery.

A clinical impression that the incidence of side effects, particularly delayed depression of ventilation, is higher after intrathecal than after epidural opioid injection is most likely the result of excessive intrathecal opioid doses.[13] For example, the analgesic effect of neuraxial opioids exerted through the receptors in the substantia gelatinosa should be the same regardless of whether the drug is placed in the epidural space and diffuses across the dura or is placed directly into the cerebrospinal fluid. On the basis of this logic, equally potent doses of opioids placed in the epidural or intrathecal space (dose about 1/10 the epidural dose) should produce similar effects at opioid receptors in the substantia gelatinosa and hence, a comparable degree of analgesia and a similar incidence of side effects due to effects of the opioid in cerebrospinal fluid.

The principal disadvantage of an intrathecal opioid injection is its lack of titratability and the need to either repeat the injection or consider other options when the analgesic effect of the initial dose wanes. Nevertheless, it is common clinical experience that after the analgesic effect of the initial intrathecal dose wanes, the intensity of postoperative pain is greatly diminished and can be satisfactorily managed with oral analgesics or PCA. The practical aspects of leaving a catheter in the intrathecal space for either continuous or repeated intermittent opioid injections is controversial, especially in view of reports of cauda equina syndrome following continuous spinal anesthesia with hyperbaric local anesthetic solutions injected through a small-diameter catheter.[14]

Epidural Administration

Epidural administration of an opioid as either an intermittent injection or a continuous epidural infusion through an epidural catheter is a common method for providing postoperative analgesia (Tables 33–4 and 33–5).[5] A low dose of local anesthetic may be added to the opioid-containing solution for injection into the epidural space. When an opioid is placed in the epidural space, it must cross the dura to reach opioid receptors in the substantia gelatinosa of the spinal cord. Besides the physical barrier presented by the dura, opioid is deposited in the fat and connective tissues present in the epidural space. The impact of these factors on the pharmacokinetics of drugs placed in the epidural space is evidenced by the estimated 10-fold increase in dose requirements for epidural opioids compared with intrathecal opioids required to produce

Table 33–4. Guidelines for Epidural Analgesia

	Bolus Dose (mg)	Onset (min)	Analgesic Peak Effect (min)	Duration (h)	Continuous Infusion Concentration (%)	Infusion Rate (ml/h)
Morphine	5	20	30–60	12–24	0.01	1–6
Meperidine	30–100	5–10	12–30	4–6		
Fentanyl	0.1	4–10	20	2–4*	0.001	4–12
Sufentanil	0.03–0.05	7	25	3*	0.0001	10
Bupivacaine†		2.5–5			0.1	4–6

* Estimate
† Combined with an opioid

a similar analgesic effect. Furthermore, the epidural space is highly vascularized, and there is significant absorption of drug into the systemic circulation. In fact, plasma concentrations of fentanyl are similar after placement of this opioid into the epidural space compared with intravenous injection (Fig. 33–3).[15] Clearly, part of the analgesic effect as well as side effects (early depression of ventilation) reflects systemic absorption of the opioid from the epidural space.

It may take as long as 3 to 4 hours to provide effective analgesia when epidural opioids are administered by intermittent injection or continuous infusion. This delayed onset of effective analgesia can readily be overcome by adjusting the infusion rate to provide the equivalent of a small bolus (5 to 10 ml) prior to beginning the maintenance infusion. Alternatively, a short-acting opioid such as fentanyl may be added to the morphine-containing solution, or the drug-containing analgesic solution can be injected preoperatively to ensure the presence of analgesia when the patient awakens at the conclusion of surgery. Bupivacaine (1 mg/ml) may also be added to the opioid-containing solution. The synergy between the analgesic effects of opioids and local anesthetics may be the result of blockade of afferent impulses at two different sites in the spinal cord. Opioids produce analgesia by binding to opioid receptors in the substantia gelatinosa, whereas local anesthetics block transmission of afferent impulses at the nerve roots and the dorsal root ganglia.

Table 33–5. Comparison of Epidural Administration Techniques

Intermittent Epidural Injection	Continuous Epidural Injection
No need for infusion devices	Needs sophisticated infusion devices
Requires personnel to inject catheter periodically	Removes need for personnel to inject catheter periodically
Limited number of suitable opioids	Allows administration of short-acting opioids such as fentanyl or sufentanil
Difficult to titrate dose	Provides continuous analgesia, avoiding peaks and valleys in the plasma opioid concentration
Higher incidence of side effects	Less rostral spread so side effects are minimized

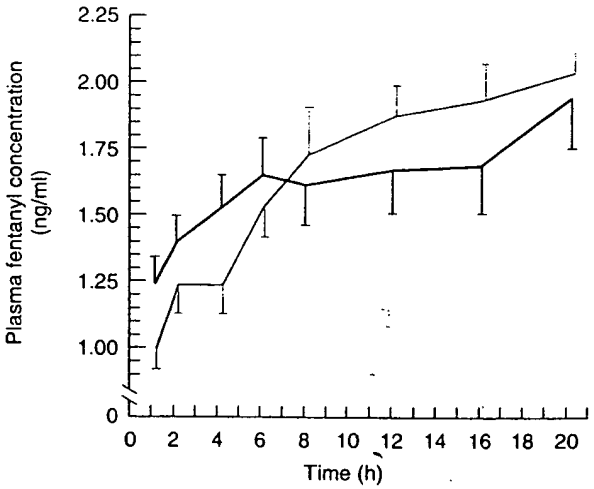


Figure 33–3. Plasma fentanyl concentrations postoperatively were similar in patients receiving lumbar epidural fentanyl infusions (red line) or intravenous fentanyl infusions (black line). (From Sandler AN, Stringer D, Panos L, et al. A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy pain relief. Analgesic, pharmacokinetic, and respiratory effects. Anesthesiology 1992;77:626–634, with permission.)

Another benefit of these combinations is a decrease in dosage of individual drugs, with a concomitant decrease in the incidence of side effects.

Postoperative Epidural Analgesia Infusion Order Sheet

- Select epidural infusion contents (morphine or fentanyl plus bupivacaine)
- Supplemental oxygen
- Monitor arterial oxygen saturations with pulse oximetry
- Observe level of consciousness and breathing rate at periodic intervals (every 1 hour may be recommended)
- Record pain score at periodic intervals
- Naloxone at bedside (administer if slow breathing rate and/or sudden decrease in level of consciousness, contact anesthesiologist)
- Morphine 2 mg IV for breakthrough pain

Intermittent intravenous injections of an opioid may be necessary to treat "breakthrough" pain until epidural analgesia is adequate. Ketorolac administration parenterally may also be a useful nonopioid analgesic in these situations. An advantage of continuous epidural infusion compared with intermittent epidural injection is the ability to titrate the infusion rate to the desired level of analgesia. It is even possible to combine a continuous epidural infusion regimen with patient-activated intermittent boluses (patient-assisted epidural analgesia). Patient-assisted epidural analgesia is particularly useful to manage dynamic changes in pain related to patient activity (coughing, chest physiotherapy). Complications that can occur with a continuous epidural technique include accidental intrathecal administration of the drug, infection, and depression of breathing.

Hydrophilic opioids such as morphine, when injected into the epidural space, result in cerebrospinal fluid concentrations of the opioid that allow the drug to follow the rostral spread of cerebrospinal fluid and saturate the entire length of the spinal cord. Because of this property, epidural morphine may be infused at a lower lumbar level and still provide analgesia for surgical procedures performed on the upper abdomen and thorax. Lipophilic opioids such as fentanyl and sufentanil tend to provide more of a segmental analgesic effect, perhaps reflecting more intense drug binding to opioid receptors. The segmental nature of analgesia produced by these lipophilic opioids is the basis for the recommendation by some anesthesiologists that the epidural catheter be placed in a position to cover the dermatomes included in the surgical field (thoracic epidural for analgesia following a thoracotomy) when a lipophilic opioid (fentanyl, sufentanil) is selected.

Achievement of optimal results with continuous epidural analgesia techniques requires appropriate perioperative planning and assessment. This strategy includes identification of patients who may benefit from epidural analgesia and scheduling the epidural catheter placement as part of the anesthetic plan. This may include epidural catheter placement in the holding area before the patient is brought to the operating room, permitting the anesthesiologist to administer a test dose of the local anesthetic (usually bupivacaine) while the patient is still awake. This facilitates diagnosis of intrathecal or intravascular placement and allows confirmation of epidural catheter placement by virtue of segmental epidural analgesia when the test dose of local anesthetic is administered. This practice also allows the continuous epidural infusion to be initiated intraoperatively (morphine or fentanyl with bupivacaine at 4 to 6 ml/h), augmenting the general anesthetic and providing sufficient time to achieve analgesia at the time of emergence from anesthesia. If the surgical procedure is expected to exceed 3 to 4 hours, sufficient solution can be infused into the epidural space to achieve analgesia on the patient's awakening. If the surgical procedure is to be less than 2 hours duration, a 5 to 10 ml dose of the epidural solution may be administered as a rapid infusion so as to hasten the onset of analgesia. Alternatively, a rapid epidural infusion of 0.5% bupivacaine combined with either fentanyl (50 to 100 μg) or morphine (2 to 5 mg) may be administered.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Prophylaxis against the occurrence of postoperative thromboembolic complications often involves the perioperative administration of low doses of subcutaneous heparin ("minidose heparin," 5000 units unfractionated heparin every 12 hours). Knowledge that this prophylaxis will be utilized may influence the anesthesiologist's decision to place an epidural catheter for postoperative pain management, as the risk of epidural hematoma formation may be increased in the presence of abnormal coagulation (Table 33–6).[16] Several large clinical studies have confirmed the safety of instituting heparin therapy in patients in whom the epidural catheter was previously placed and in whom clinically detectable bleeding was absent at least 1 hour.[17, 18] Postponement of surgery for 24 hours may be recommended if placement of the epidural catheter is associated with a bloody tap. Timing of removal of the epidural catheter is also considered to be critical as epidural bleeding could be initiated at this time. In this regard, it is often recommended that removal of the epidural catheter occur 10 to 12 hours after the last dose of heparin and subsequent dosing with heparin be delayed for at least 1 hour after removal of the cathe-

Table 33–6. Recommendations for Performance of Neuraxial Analgesia/Anesthesia in the Presence of Anticoagulants Administered for Thromboembolism Prophylaxis or Intraoperative Coagulation

Unfractionated (standard) minidose subcutaneous heparin
No contraindication to neuraxial block
May consider delaying initiation of heparin therapy until after neuraxial block
Unfractionated (standard) intravenous heparin for intraoperative coagulation
Delay initiating heparin administration for 1 hour after needle placement for the neuraxial block
Remove the epidural catheter 1 hour before any subsequent intravenous dose of heparin (assumes a 12 hour dosing interval) or 2 to 4 hours after the last previous dose of heparin
Consider the use of minimal concentrations of local anesthetic to permit early clinical detection of neurologic changes
Blood or difficult neuraxial needle and/or catheter placement does not mandate cancellation of the surgical procedure but if it proceeds must perform frequent postoperative monitoring of neurologic status
Low molecular weight heparin
Decision to perform a neuraxial block is made on an individual patient basis
Bloody or difficult neuraxial and/or catheter placement does not mandate cancellation of the surgical procedure but if it proceeds should delay initiation of low molecular weight heparin administration for 24 hours
Delay epidural catheter removal for 10 to 12 hours after the last dose of low molecular weight heparin and do not administer any subsequent doses of heparin for 2 hours
Consider single dose spinal anesthesia if regional anesthesia is required in patients receiving low molecular weight heparin preoperatively
Perform frequent postoperative monitoring of neurologic status
Oral anticoagulants
Stop anticoagulant and allow normalization of prothrombin time before performance of neuraxial block
Antiplatelet drugs
Use does not interfere with the performance of a neuraxial block
Fibrinolytic and thrombolytic drugs
Neuraxial block not recommended within 10 days of receiving these drugs

(Modified from Neuraxial Anesthesia and Anticoagulation, Consensus Statements. American Society of Regional Anesthesia, 1998.)

ter (Table 33–6).[16] Patients must be monitored closely in the perioperative period, including the time following catheter removal, for early signs of cord compression (back pain, progression of numbness or weakness, bowel or bladder dysfunction) from a developing epidural hematoma. Prompt recognition of an epidural hematoma (confirmed by computed tomography or magnetic resonance imaging) is followed by a decompressive laminectomy. Recovery of spinal cord function is unlikely if surgery is delayed more than 8 hours.[19]

In contrast to unfractionated heparin, low molecular weight heparin was intended to provide the potential for separating the antithrombotic from the bleeding effects of heparin. However, reports of epidural hematoma occurring spontaneously and in association with regional anesthesia have created concern regarding the safety of spinal or epidural anesthesia in patients receiving low molecular weight heparin (Table 33–6).[16] The same concerns would also seem to apply to these regional techniques as utilized for neuraxial analgesia.

MANAGEMENT OF INADEQUATE ANALGESIA. In the presence of inadequate analgesia provided by the epidural infusion, it is important to verify the proper placement of the catheter. The initial step is the rapid epidural infusion of 5 to 7 ml of the opioid and local anesthetic solutions. If analgesia remains inadequate after 15 to 30 minutes, a test dose of a local anesthetic solution, such as 2% lidocaine with 1:200,000 epinephrine, can be administered to further evaluate catheter location. If this test dose produces a bilateral sensory block in a few segmental dermatomes, epidural catheter location is confirmed. Based on this observation, it is presumed that the rate of epidural infusion was insufficient for adequate analgesia and that increasing the rate of infusion may produce acceptable analgesia. If the test dose of local anesthetic solution produces a unilateral sensory block, it is likely the catheter is placed laterally and withdrawal of the catheter 1 to 2 cm is indicated. A lack of sensory block in response to the local anesthetic solution test dose confirms the catheter is not in the epidural space.

In this situation, the catheter is removed and the patient is given the option of having another epidural catheter placed or switching to PCA therapy.

ALTERNATIVE APPROACHES TO MANAGEMENT OF ACUTE POSTOPERATIVE PAIN

Alternative approaches to analgesia delivery systems for treatment of acute postoperative pain include peripheral nerve blocks, intrapleural regional analgesia, and transcutaneous electrical nerve stimulation (TENS).

Peripheral Nerve Blocks

Peripheral nerve blocks may provide effective postoperative analgesia, but their relatively short duration of analgesia and their selective nature preclude their general application to all patient populations. Nevertheless, pain relief afforded by a regional nerve block may be superior to that achievable with systemic opioids. For example, intercostal nerve blocks may be useful for providing postoperative analgesia after abdominal or thoracic operations (see Chapter 14).

Intrapleural Regional Analgesia

Intrapleural regional analgesia is produced by injection of local anesthetic solution through a catheter placed percutaneously into the intrapleural space. The local anesthetic diffuses across the parietal pleura to the intercostal neurovascular bundle, producing a unilateral intercostal nerve block at multiple levels. Effective postoperative pain relief requires intermittent intrapleural injections approximately every 6 hours with approximately 20 ml of 0.25% to 0.5% bupivacaine. Pleural drainage tubes as placed following a thoracotomy may result in loss of the local anesthetic solution and inadequate analgesia.

Transcutaneous Electrical Nerve Stimulation

TENS is a simple conservative technique that utilizes electrical stimulation of the skin to provide pain relief (see Chapter 35). The mechanism by which TENS produces pain relief is presumed to involve the release of endogenous endorphins by the electrical stimulation of afferent cutaneous nerves. Endorphins exert an inhibitory effect on the dorsal horn and augment the descending inhibitory modulating pathways. The degree of acute pain relief provided by TENS is variable and less effective than that produced by neuraxial opioids or PCA.

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